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Learning from Prozac: A Case Study on Reforming the FDA Drug Approval
Process

Submitted to Professor Peter B. Hutt
in the Food and Drug Law Winter Course
in Satisfaction of the Written Work Requirement

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I. Introduction

Since the early 1990s, the Food and Drug Administration (FDA) has been embroiled in a wide-ranging social debate taking place from the legal literature to the halls of Congress over the proper parameters of its regulatory authority over the drug approval process.¹ Addressing the many concerns driving the debate, Dr. David Kessler promised to make the FDA work better and more efficiently when he stepped up to its helm as Commissioner in 1991.² With that commitment and with pressure from AIDS activists and Republican members of Congress, the FDA began reforming its approval process for new drugs in order to decrease the amount of time required for a new drug to reach the market. By enacting measures designed to decrease the amount of study

For a sample of this debate, see generally George J. Annas, *Faith (Healing), Hope*

and *Charity at the FDA. The Politics of AIDS Drug Trials*, 34 VILL. L. REV. 771 (1989); C.

Frederick Beckner, 111, Note, *The FDA's War on Drugs*, 82 GEO. L.J. 529 (1993); John P.

Dillman, *Terminal Diseases.* 'Desperate Times Require Desperate Measures', 44 VAND. L. REV.

925 (1991); Veronica Henry, *Problems with Pharmaceutical Regulation in the United States*, 14

J. LEGAL MED. 617 (1993); Eric M. Katz, *Europe's Centralized New Drug Procedures: Is the*

United States Prepared to Keep Pace?, 48 FOOD & DRUG L.J. 577 (1993); John M. Mendeloff

Decision Analysis and FDA Drug Review. 'A Proposal for 'Shadow' Advisory Committees', 6

RISK: HEALTH SAFETY & ENV'T 203 (1995); Beth E. Myers, *The Food and Drug*

Administration's Experimental Drug Approval System: Is It Good for Your Health?, 28 Hous.

L. REV. 309 (1991); Note, *FDA Reform and the European Medicines Evaluation Agency*, 108

HARV. L. REV. 2009 (1995); Elizabeth C. Price, *Teaching the Elephant to Dance.* 'Privatizing

the FDA Review Process, 51 FOOD & DRUG L.J. 651 (1996); Julie C. Relihan, *Expediting FDA*

Approval of AIDS Drugs. 'An International Approach', 13 B.U. INT'L L.J. 229 (1995); Elizabeth

M. Rutherford, *The FDA and Privatization — The Drug Approval Process*, 50 FOOD & DRUG L.J.

203 (1995); and, Charles J. Walsh and Alissa Pyrich, *Rationalizing the Regulation of Prescription*

Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform, 48

RUTGERS L. REV. 883 (1996).

The debate has involved all of the FDA's regulatory powers, not merely its authority over the entrance of new drugs onto the market; however, this paper will only consider the debate on reform as it relates to the drug approval process.

² See Price, *supra* note 1, at 651.

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that some new drugs must undergo in order to be considered safe and effective and by reorganizing itself internally to ensure faster review of drugs awaiting approval, the FDA has posted decreases in the amount of time taken for a new chemical entity to reach the final stage of approval for marketing.³ This apparent success has not appeased the agency's critics, however, and commentators have noted that further reform seems likely.⁴

An analysis of the current drug approval process as it was implemented to approve the controversial antidepressant Prozac will demonstrate that the current system has significant deficiencies which current reform proposals do not address. For example., the FDA approved Prozac without a good indication that it would be effective in treating depression and without adequate information on the adverse effects it would cause.⁵ The lessons learned about Prozac's process will show the reforms that are needed in order to remedy some of the current shortcomings in the system.

An analysis of the controversy surrounding Prozac will also demonstrate why currently discussed proposals will fail to realize a reformed drug approval process that is acceptable to the American public. In the midst of the reform debate, commentators have focused their analyses on the regulatory process without considering the more informal process of public drug approval.⁶

See infra, notes 189-197 and accompanying text.

See, e.g., Note, *supra* note I, at 2026 (noting that the firestorm of attention directed at the FDA's drug approval process in recent months strongly suggests that *some* change will take place).

See infra, notes 150-153 and accompanying text. *See also, infra* notes 158-167 and accompanying text.

⁶ *Infra*, part [II].

The American experience with Prozac illustrates the effect that this informal process has on American consumers and demonstrates that the current proposals for reform are misguided and too narrowly focused in failing to account for it.

In conducting this case study, special attention will be paid to the scientific issues involved. Failing to consider these issues means that any proposal offered risks being legal without being scientifically valid.⁷ In developing a reform proposal based on an understanding of Prozac, then, the scientific issues will be explored in an effort to account for the technical aspects of drug development and approval

Toward these ends, Part II will outline the current drug approval process. Part III will examine the history of Prozac since its introduction onto the market and will analyze the specific process that Prozac underwent to obtain approval. Part IV will summarize the current state of the debate regarding reform at the FDA, outlining the major reform proposals currently being advocated and showing why they are deficient. Part V will develop a proposal for reform that takes account of the lessons learned from Prozac. From this case study and the lessons learned from experience with Prozac, this paper will conclude that reform of the FDA's drug approval process should proceed along a careful course that addresses the reforms needed for specific categories of drugs and that achieves public acceptance of decisions made by the FDA.

The law, focused as it is on making final determinations and settling issues one way or another, continually lags behind science, which concentrates on an evolving understanding of various phenomena through constant enhancement of current understandings of existing realities. Thus, a drug approval process, which obviously deals with scientific issues of drug development, cannot always keep pace with scientific understandings of drug development. The law is flexible and capable of accommodating new understandings, though; therefore, consideration of the scientific issues involved in drug development and approval is appropriate and ought to be undertaken as much as possible in order to develop legal answers that are as accurate as they can be at any given time.

IL The FDA Drug Approval Process

A. Background

The FDA's authority to require premarket testing and approval of new drugs derives from the Federal Food, Drug and Cosmetic Act (FDCA), which mandates that no person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application. . is effective with respect to such drug.⁴ In order to obtain the approval necessary for marketing, the application must contain information related to the composition, manufacturing and labeling of the drug and reports showing safety and effectiveness of the drug.⁹ Once approved, the application becomes effective and the drug may be sold.

The rationale behind the legislation can be understood as a regulatory response to a market failure.¹⁰ The failure arises because drug manufacturers, interested primarily in getting

8 21 U.S.C.A. §355(a) (West Supp. 1973-1995). A thorough understanding of the

drug approval process requires understanding not only the rules and regulations of the process but also the historical context in which they were developed; however, an explication of the historical context exceeds the scope of this paper. For a history of the FDCA and its evolution from a statute granting limited authority to the FDA to allow new drug applications to become effective to a statute mandating extensive FDA involvement in the review and approval of new drugs, see Peter Barton Hurt and Richard A. Merrill, *Food AND DRUG LAW: CASES AND MATERIALS* 475-487 (1991). *See also*, James R Nielsen, *HANDBOOK OF FEDERAL DRUG LAW* 3-12 (2d ed. 1992) (summarizing the history of federal drug law).

21 U.S.C.A. §355(b)(1) (West Supp. 1973-1995). The requirement of efficacy was added to the statute in 1962 through the Kefauver-Harris Amendments to the Food and Drug Act, in response to what has been called the thalidomide tragedy. Hutt and Merrill, *supra* note 8, at 478. Thalidomide, a drug for pregnant women, was introduced onto the market in Great Britain, and was quickly shown to cause severe birth defects in the fetuses of those women. *Id* at 452.

10 Beckner, *supra* note 1, at 530 (citing Sidney A. Shapiro and Joseph P. Tomain,

REGULATORY LAW AND POLICY 467-68 (1993) and Paul J. Quirk, *Food and Drug Administration, in* THE POLITICS OF REGULATION 191, 191-192 (James Q. Wilson ed., 1980)).

their products onto the market quickly, lack sufficient incentive to conduct the tests necessary to provide full information on their products. Furthermore, any information available is generally too scientifically complex for the average consumer; thus, the consumer cannot make an informed choice regarding a proposed drug treatment. A regulatory agency is therefore necessary to facilitate the consumer's decisions regarding the important elements of a drug choice – whether the drug is safe for use and effective in treating the intended problem. The American response has been the creation of an elaborate statutory and regulatory framework administered by the FDA.

B. The Premarket Approval Process

The regulatory framework established for approving new drugs requires a sponsor¹² to demonstrate that the drug is both safe and effective. The procedure for approval can be broken down broadly into three stages: (1) application for approval to conduct clinical trials of an investigational new drug (IND), (2) clinical testing and submission of a new drug application

Throughout this paper, the terms patient and consumer¹³ will be used synonymously, and consumer will never be used to refer to a physician. The distinction is important to keep in mind. Some authors and drug companies refer to the physician as the consumer because the physician selects a particular drug from among the available options. Ultimately, however, it is the patient who makes the purchase, consumes the drug, and bears any risks and benefits associated with its use. Moreover, except in emergencies, physicians must obtain the patient's informed consent to any proposed treatment; thus, the patient, theoretically at least, makes the actual purchase decision. *See* Clark C. Havighurst, HEALTH CARE LAW AND

POLICY: READINGS, NOTES, AND QUESTIONS 18 1-82 (1988) (discussing the agency problem in the physician-patient relationship).

¹² Sponsor is the term given by FDA regulations to the person or agency who assumes responsibility for compliance with applicable provisions of the [FDCA] and regulations. The 'sponsor' may be an individual, partnership, corporation, or government agency and may be a manufacturer, scientific institution, or an investigator. 21 C.F.R. §310.3(j) (1996). This paper will use the terms sponsor, company and manufacturer interchangeably.

(NDA), and (3) FDA evaluation of and response to the NDA.

I. [ND Stage]

Drug development begins with the identification of a new chemical entity (NCE) that shows promise as a treatment for some human condition. Under the FDCA, the FDA may require the sponsor to provide any pre-clinical testing data that is adequate to justify the proposed clinical testing.¹³ Therefore, the NCE undergoes rigorous testing in animals designed to determine whether or not it has the potential to be safe and effective when used in humans. Currently, pre-clinical testing takes approximately thirty months and focuses on evaluating the toxicology¹⁴ and pharmacology¹⁵ of the NCE.¹⁶ Ultimately, the data from animal testing must make predictions as to an NCE's safety and its toxicity in humans and must establish that it is likely to have therapeutic value in humans¹⁷

Having established that the NCE has potential therapeutic value and is probably safe and effective when used by humans, the company files a Notice of Claimed Exemption for an Investigational New Drug ([ND]), which allows shipment of the drug in interstate commerce for

¹³ 21 U.S.C.A. §355(k)(1) (West 1972).

Toxicology is concerned with toxic substances, detecting them, studying their chemistry and pharmacological actions, and establishing antidotes and treatment of toxic manifestations, prevention of poisoning, and methods for controlling exposure to harmful substances. *TABER'S CYCLOPEDIA MEDICAL DICTIONARY* 1974 (Clayton L. Thomas, ed., 18th ed. 1997).

¹⁵ Pharmacology is the study of drugs and their origin, nature, properties, and effects upon living organisms. *Id.* at 1461.

¹⁶ Walsh and Pyrich, *supra* note 1, at 905.

¹⁷ *Id.* (citing 51 Fed. Reg. 36,558 (1986), to be codified at 21 C.F.R. §1308).

the purpose of conducting clinical trials.’⁸ The IND must contain all of the following information:

identification of the drug to be tested; detailed information currently known about the drug, including information gathered when the drug is used in other countries; a detailed outline of the proposed clinical investigations that will take place; and, data from pre-clinical testing, including adequate pharmacology and toxicology information, that demonstrate that testing in humans will be reasonably safe.’⁹ Though the FDA can refuse to allow an IND to go into effect it; in its judgment, important information is lacking, the IND generally takes effect automatically, thirty days after the FDA receives it. Once the IND is in effect, the company can begin clinical trials.²⁰

2. Clinical Testing and NDA Stage

Clinical testing proceeds according to the plan outlined in the IND.²¹ The testing begins with Phase I trials, which are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.²² A small group of healthy volunteers receives the drug, first in single doses, which, if tolerated, are followed by administration of multiple doses. The

²¹ C.F.R. §312.1(a)(1996).

²¹ C.F.R. §312.23 (1996).

²⁰ 21 C.F.R §312.40(b)(1)(1996).

²¹ Currently, the FDA has no binding regulations that define what scientific methods of testing will be acceptable to the agency. The FDA has issued guidelines that establish principles or practices of general applicability related to, among other things, preclinical and clinical testing procedures and that provide model protocols for scientific testing. 21 C.F.R. § 312.23(b)(1) (1996). A sponsor who uses these model protocols is assured that doing so will be acceptable to the FDA, but the sponsor is not required to use them. 21 C.F.R §312.23(b)(1)(1996).

²² 21 C.F.R §312.21(a)(1996).

investigators collect data on the adverse effects associated with the drug and do not usually concern themselves with determining the drug's efficacy.²³

Assuming that no serious adverse effects are found, the sponsor proceeds with Phase [I] trials to evaluate the effectiveness of the drug for a particular indication or indications in patients

and to determine the common short-term side effects and risks associated with the drug.²⁴ Small numbers of patients who have the disease the drug is designed to treat receive the drug and intensive investigations are conducted analyzing their response to it. The tests attempt to determine whether the drug has the desired therapeutic effect, the dose range at which this effect occurs, and whether any adverse effects observed will limit the drug's usefulness.²⁵

Phase [II] trials are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.²⁶ In this phase of testing, a larger population sample of patients who have the disease the drug is intended to treat receive the drug. The sponsor tests the drug in comparative studies, using a placebo or a standard drug treatment, to determine whether or not the new drug has the intended effect. From these data, the sponsor makes a determination of what adverse effects will accompany use of the drug and a preliminary determination of what

²³ Hutt and Merrill, *supra* note 8, at 516.

²⁴ 21 C.F.R. §312.21(b)(1996).

²⁵ Hutt and Merrill, *supra* note 8, at 516.

²⁶ 21 C.F.R. §312.21(c)(1996).

interactions might result from use of the new drug with other medications.

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After the clinical testing is complete, the sponsor compiles all favorable and unfavorable information that is known about the drug into an NDA. FDA regulations require that the NDA include the preclinical data on pharmacology and toxicology, the results of the clinical test data, an analysis of the risks and benefits that should be considered, and a statistical evaluation of the clinical data.²⁸ The sponsor then forwards the NDA to the FDA for review.

3. NDA Review

Once the FDA has received the NDA, the NDA is reviewed by one of five of the Offices of Drug Evaluation. Each of these offices oversees the review and approval of drugs for certain medical conditions.²⁹ The FDA has 180 days³⁰ from receipt of an NDA to review and take action on it. FDA approval requires primarily that the preclinical and clinical test data show that the

drug is safe for use under the conditions prescribed, recommended, or suggested in the

labeling³¹ and that there be substantial evidence that the drug will have the effect it purports to or is represented to have under the conditions of use prescribed, recommended, or suggested in

27 Hurt and Merrill, *supra* note 8, at 516.

28 21 C.F.R. §314.50(d)(1996).

29 Tamar Nordenberg, *Inside FDA: The Center for Drug Evaluation and Research*, FDA CONSUMER, July-Aug. 1996, available at http://www.fda.gov/fdac/features/696_cder.html.

30 21 U.S.C.A. §355(c)(1) (West Supp. 1973-1995). The period for review can be extended for longer than 180 days if the applicant agrees. 21 C.F.R. §314.100(c) (1996).

31 21 U.S.C.A. §355(d)(1) (West Supp. 1973-1995).

the labeling.³² The statute defines substantial evidence as evidence consisting of adequate and well-controlled investigations, including clinical investigations undertaken by experts in the field.³³ The FDA has interpreted the statutory requirement of adequate and well-controlled investigations to mean that the sponsor must provide at least two adequate and well-controlled studies showing efficacy in order for the drug to be approved.

If the FDA's review shows that the drug is safe, that two studies find that it is effective, and that other requirements, such as for manufacturing and labeling, meet statutory standards, the FDA will issue the sponsor an approval letter, which permits marketing of the drug.³⁴ In some cases, the FDA may believe that it can approve the NDA provided certain outstanding issues are solved. In that situation, the FDA will issue an approvable letter. Approvable letters are sent if the [NDA] substantially meets [FDA] requirements and the agency believes that it can approve the [NDA] if specific additional information or material is submitted or specific conditions (for example, certain changes in labeling) are agreed to by the [sponsor].³⁵ The sponsor must respond within ten days and, upon response, the review period is extended for 45 days.³⁶

³² 21 U.S.C.A. §355(dX5) (West Supp. 1973-1995).

³³ 21 U.S.C.A. §355(d) (West Supp. 1973-1995). Adequate and well-controlled investigations are defined by regulation. 21 C.F.R §312.125 (1996). It has been suggested that the substantial evidence burden of proof for efficacy is somewhat low and not intended to erect an insurmountable barrier for promising new drugs. Note, *supra* note I, at 2019 (explaining that in adopting the 1962 Kefauver-Harris Amendments, Congress rejected a higher preponderance of the evidence standard in favor of substantial evidence).

³⁴ 21 C.F.R §3 14. 105 (1996).

³⁵ 21 C.F.R §314.110(a)(1996).

³⁶ *Id*

The FDA will refuse to approve an NDA if the drug is not proved to be both safe and effective. The FDA may also refuse to approve an NDA on other grounds, such as the failure of the manufacturing and processing methods to insure that the drug retains its identity, strength, quality and purity; omission of data, or failure to correct prior deficiencies.³⁸ If the application is not approved, the applicant receives notice and an opportunity for a hearing.³⁹

C. Postmarketing Regulation

After approval of an NDA and marketing of the new drug, the drug's sponsor continues to have responsibilities to the FDA. In some cases, the FDA will condition its approval on the sponsor's agreeing to conduct long-term studies to determine the drug's effects in chronic-use patients.⁴⁰ These tests, called Phase IV trials, are used when long-term safety and effectiveness data is needed but the necessity of the drug or its potential benefit does not justify a delay in putting the drug on the market.

By law, the manufacturers, packers and distributors of drugs must maintain records and make reports to the FDA of adverse effects⁴¹ that occur in connection with the use of the new

21 U.S.C.A. §355(d)(3) (West Supp. 1973-1995).

38 21 C.F.R. §314.125 (1996).

21 U.S.C.A. §355(d) (West Supp. 1973-1995).

40 21 C.F.R. §310.303 (1996).

Adverse effects are symptoms or problems that develop in connection with the use of a drug. They are called adverse effects, adverse events, adverse experiences, or side effects. Adverse drug reactions (ADRs) are adverse events that are causally linked with the use of a drug.

drug and of therapeutic failure of the drug.² Reports to the FDA of serious adverse effects must occur within fifteen days of a health professional or consumer reporting an adverse effect to the company. The company must review all reports received at least annually and submit reports to the FDA of that review.³ The FDA requires these reports and records in order to provide it with the data necessary to determine whether or not there are grounds for withdrawing the drug from the market. If any new evidence indicates that the drug is unsafe or ineffective, the FDA will require the sponsor to withdraw the drug from the market.⁴

In addition to requiring reports of adverse effects from the drug companies themselves, the FDA also accepts reports of adverse effects from health care professionals and consumers. Called spontaneous reporting or voluntary reporting, health care professionals and consumers have always been able to contact the FDA with reports of adverse events that occurred while a patient/consumer was taking a drug or using a medical device. The FDA has focused its efforts, though, on obtaining reports from health professionals rather than consumers.

In 1993, the FDA, concerned that health professionals were not reporting ADRs, renewed its commitment to accepting such reports and began a program designed to encourage and stimulate the reporting of adverse drug events by physicians and other health professionals. Toward this end, the FDA announced in the Federal Register a new form for reporting adverse effects as part of its new MEDWATCH, Medical Products Reporting Program, which has as its primary focus to inform and encourage health professionals (physicians, physician assistants,

⁴² 21 C.F.R §310.305(a)(1996).

²¹ C.F.R §310.305(c) (1996).

²¹ U.S.C.A. §355(e) (West Supp. 1973-1995).

pharmacists, nurses, and others) about reporting serious adverse events and product problems.⁵ The FDA began this program because voluntary reports from health care professionals are

an essential means of facilitating the FDA's monitoring of the safety of the drugs on the market.⁴⁶ By providing an easier form to use for reporting and by embarking on a nationwide education program for health care professionals on the importance of reporting, the FDA hoped to stimulate voluntary reporting.⁴⁷ To implement the new program, the FDA has used many strategies: presentations and exhibits at the conferences and meetings of health professional associations, explaining MED WATCH and the importance of reporting; development and implementation of training curricula for health professionals to educate them on detecting ADRs; distribution of a single, postage-paid form for reporting all types of adverse drug and device effects; and improvement of the feedback system for MEDWATCH, by providing regular updates on product problems through the FDA Medical Bulletin and a quarterly MEDWATCH update⁴⁸

58 Fed. Reg. 31596, 31596 (1993).

46 David A. Kessler, *Introducing MED Watch: A New Approach to Reporting Medication and Device Adverse Effects and Product Problems*, 269 JAMA 2765, 2765 (1993). MEDWATCH does not appear to focus its efforts on information relating to efficacy. Health professionals are encouraged to report only serious, adverse events, defined *infra*, related to drug usage, suggesting that the primary purpose of the program is to monitor the safety of drugs on the market.

58 Fed. Reg. 31596, 31597 (1993). Compared with other countries that operate a voluntary reporting system, US reporting rates have been very low. Gerald A. Faich, *Adverse Drug-Reaction Monitoring*, 314 NEW ENG. J. MED. 1589, 1592 (1986) ('The rate of adverse-reaction reporting in the United States is far below that in many other developed countries') (citation omitted). Dr. Kessler estimated that only one percent of serious adverse events are reported to the FDA. Kessler, *supra* note 46, at 2765 (citation omitted).

48 Justina A. Moizon, *The FDA's Perspective on the Future of Pharmacy*, 44 DRAKE

L. REv. 463, 467-8 (1996). As technology has become available, the FDA has implemented (continued...)

The FDA encourages only the reporting of serious adverse effects, which it defines as those cases in which the physician suspects that an FDA-regulated product was associated with a serious outcome – death, a life-threatening condition, initial or prolonged hospitalization, disability, or congenital anomaly, or when intervention was required to prevent permanent impairment or damage.⁴⁹ The FDA also emphasizes reporting events that occur with drugs that have been on the market for less than three years, because this appears to be the critical time period in which most serious problems are discovered.⁵⁰ Though the FDA considers the program voluntary, various organizations within the medical community have begun imposing an obligation on their members to make MEDWATCH reports.⁵¹

The FDA has recently amended its regulations to preempt state and local laws that might require or permit disclosure of the identities of those who report adverse events to either the FDA

48(.. continued)

electronic means of filing reports, such as providing a toll-free fax number. Forms for reporting can also be obtained on the Internet. *See* MEDWATCH Home Page. at <http://www.fda.gov/medwatch/report/hcp.htm>.

Kessler, *supra* note 46, at 2768.

SO *Id*

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), the primary accrediting organization for hospitals and health maintenance organizations (HMOs), requires its organizations to set up a system for reporting adverse drug events in order to receive accreditation. American Medical Association, *Reporting Adverse Drug and Medical Device Events.* *Report of the AMA's Council on Ethical and Judicial Affairs*, 49 *Food & Drug L.J.* 359, 362 (1994). Additionally, the American Medical Association has amended Principle V of its Code of Medical Ethics to impose an ethical obligation on physicians to report adverse reactions to the appropriate authorities. *Id* at 362-3. The FDA encourages medical professionals to regard reporting as a fundamental professional and public health responsibility, Kessler, *supra* note 46, at 2767, but does not impose the obligation.

or the manufacturer.⁵² The regulation now gives the FDA complete authority to protect the confidentiality of adverse reaction reports. The FDA promulgated it in part to encourage adverse reaction reporting, because it was generally assumed that low US reporting rates were linked with physicians' fears that the report would constitute an admission of liability for a patient's drug injury if the report were discovered in a medical malpractice suit.⁵³ Despite assurances from the FDA that it would protect a MED WATCH reporter's confidentiality,⁵⁴ reporters now receive absolute protection from having their identities released in connection with an adverse reaction report.

The FDA has made no systematic attempt to collect adverse reaction reports from consumers,⁵⁵ and a program similar to MEDWATCH for consumers does not currently exist. The FDA's position on consumer reporting has been to accept reports from consumers but to

⁵² 60 Fed. Reg. 16962 (1995).

H. Denman Scott et al, *Physician Reporting of Adverse Drug Reactions.* *Results of the Rhode Island Adverse Drug Reaction Reporting Project*, 263 JAMA 1785, 1786 (1990) (discussing reasons behind health care professionals' failure to report adverse drug reactions).

Kessler, *supra* note 46, at 2767 the FDA carefully protects the identities of providers who report. ... [The FDA] has participated in a number of court cases vigorously opposing release of the names of those involved in adverse event reports. To date, we have been successful in maintaining the confidentiality of this information in all the cases in which we have been involved).

There have been some studies conducted to determine the feasibility and reliability of consumer reports, in which adverse reaction reports were collected directly from consumers. *See infra*, notes 285-296 and accompanying text. In addition, the FDA's MEDWATCH Home Page on the Internet provides instructions to consumers for filing adverse event reports. Consumers are encouraged to file their reports through their physician, by downloading a report form and taking it to their physician. If the consumer does not wish to go through the physician to file, the Home Page provides instructions for downloading the form and filling it out. MEDWATCH Home Page, *available at* <http://www.fda.gov/medwatch/report/consumer/consumer.htm>.

encourage consumers to report through their physicians and to make no effort to stimulate consumer reporting. The agency has stated that consumers are encouraged to work with their health professionals to submit the MED WATCH form.⁵⁶

111. The History of Prozac

In addition to the regulatory process of drug approval, new drugs also undergo an informal process of public drug approval that determines whether or not the FDA's judgments about safety and efficacy will be upheld. A survey of the history of Prozac since FDA approval shows that this process has huge social costs because the results are often mixed. Following Prozac's approval for marketing in December 1987, controversy over its safety led consumers to question their physicians^t judgment, forced Prozac's manufacturer⁵⁷ to pour out resources to defend the drug in court and in the media, caused the FDA to waste resources justifying its findings about the safety and efficacy of Prozac, and made physicians defend themselves against malpractice liability for prescribing a drug that had already undergone an elaborate and expensive procedure to establish the propriety of prescribing it.

Prozac was the first of a new class of drugs called selective serotonin reuptake inhibitors (SSRIs) to be approved by the FDA.⁵⁸ The development process for Prozac[~] was expensive and

⁵⁶ 58 Fed. Reg. 31596, 31599 (1993).

Prozac's manufacturer was Eli Lilly & Company (hereinafter Lilly).

⁵⁸ SSRIs make more serotonin available in the brain by acting to inhibit the uptake of serotonin, a neurotransmitter in the brain. Known chemically as 5-hydroxytryptamine, serotonin is one of many neurotransmitters, substance[s]... manufactured by a cell. Michael K. Trimble, BIOLOGICAL PSYCHIATRY 68 (2d ed. 1996). A neuron releases a neurotransmitter and transmits it to another neuron, thereby causing the second neuron to fire. The firing of neurons drives activity in the brain, making human voluntary and involuntary functions possible. *See id* at 41-75

(continued...)

time-consuming. Prozac spent fifteen years and seven months in development before receiving approval from the FDA to be marketed in the United States. Discovered in May 1972, the first results of animal tests were not published until two years after discovery.⁶⁰ Seven years of clinical testing followed after two additional years of preclinical animal testing, and in the fall of 1983 Lilly submitted an NDA for fluoxetine.⁶¹ Once the NDA reached the FDA, the drug spent four years awaiting approval. By October 1985, the Psychopharmacological Drugs Advisory Committee, a panel of experts responsible for reviewing the data submitted on new psychopharmacological drugs and recommending action to the FDA, had recommended approval,⁶² but the FDA did not indicate that the application for fluoxetine was approvable until

SS(.continued)

(providing a basic understanding of the physiology and chemistry of the brain). For an explanation of SSRIs and their action on neurotransmitters, see B.E. Leonard, *Second Generation*

Antidepressants. Chemical Diversity but Unity of Action?, in PSYCHOPHARMACOLOGY OF

DEPRESSION (Stuart A. Montgomery and Timothy H. Corn, eds., 1994).

Scientists believe that serotonin levels are linked with depression, *see infra*, note 171 and accompanying text; thus, by making more serotonin available in the brain, SSRIs combat a patient's depression.

Prozac is the brand name for the chemical compound fluoxetine, which, when synthesized for human use, is labeled fluoxetine HCl. Throughout this paper, the term fluoxetine will be used in lieu of Prozac when discussing scientific evidence or medical information, as this is the name scientists use in their discussion papers. The use of the name Prozac will refer to the drug as prescribed and as it is known by the American public.

60 Jerrold F. Rosenbaum, *Clinical Trial by Media: The Prozac Story*, in PSYCHIATRIC PRACTICE UNDER FIRE: THE INFLUENCE OF GOVERNMENT, THE MEDIA AND SPECIAL INTERESTS ON SOMATIC THERAPIES 3, 6 (Harold I. Schwartz, ed., 1994).

61 *Id.*

62 *Id.*

September 1987.⁶³ Final approval followed in December 1987.

A. The Rise and Fall of Prozac

At first, the informal process of public approval accepted Prozac. The drug posted record sales and attracted unprecedented public attention. By the end of 1988, after Prozac had been on the market for only one year, the new drug was posting sales of \$125 million.⁶⁴ At the end of 1989, Prozac's sales volume had increased by 280%, up to \$350 million for the year.⁶⁵ Analysts projected that Prozac would bring in \$500 million in 1990 and over \$1 billion annually by 1995.⁶⁶

Driving Prozac's sales growth was its popularity with physicians, who tended to prefer it over the older antidepressants because of two significant advantages. First, Prozac caused none of the uncomfortable side effects, such as dry mouth, blurred vision, racing heartbeat, constipation, cognitive impairment and weight gain, that were associated with older antidepressants and that discouraged patients from continuing with those medications.⁶⁷ While Prozac was associated with some side effects, including nervousness, insomnia and gastrointestinal distress, patients generally tolerated these symptoms better. As a result, patients were more compliant with drug therapy, remaining on the drug until there was a therapeutic

⁶³ Judith Valente, *Eli Lilly's New Antidepressant Drug Clears FDA Hurdle, Stock Jumps \$10*, WALL ST. J., Sept. 14, 1987, available in WESTLAW, 1987 WL-WSJ 304484.

⁶⁴ Geoffrey Cowley, *The Promise of Prozac*, NEWSWEEK, Mar. 26, 1990, available in LEXIS, News Library, Arcnws file.

⁶⁵ *Id*

⁶⁶ *Id*

⁶⁷ Rosenbaum, *supra* note 60, at 6.

effect.⁶⁸ Consequently, treatment for depression was more likely to be successful. A second major advantage of Prozac was the inability of a patient to use the drug to commit suicide.⁶⁹ Physicians thus felt much freer to prescribe the drug to their patients, some of whom may be suicidal, because of the reduced risk that the medication could be abused. ~

The public also began to seek out Prozac, asking their physicians to prescribe it for them and, in some cases, switching physicians if they were turned down.⁷¹ By the end of 1990, approximately three million patients had taken or were taking Prozac.⁷² Media attention, with its promises of miracles, had fanned the flames and sparked intense public interest in Prozac. Responding to the record sales and the significant advancement in the treatment of depression, the media began to flaunt the virtues of Prozac. *New York Magazine*⁷³ and *Newsweek*⁷⁴ both extolled the virtues of Prozac and stories began to emerge of patients, previously incurable, for whom Prozac had worked a miracle.⁷⁵ Though the reports generally presented a balanced consideration

68 *Id* Antidepressant drug therapy is generally believed to require several months of treatment before a patient's depression lifts. *See infra*, note 132.

69 *See infra*, notes 133-136 and accompanying text.

70 Cowley, *supra* note 64.

71 *Id*

72 Rosenbaum, *supra* note 60, at 10.

Rosenbaum, *supra* note 60 (citing F. Schumer, *Bye-Bye Blues: A New Wonder Drug for Depression*, NEW YORK MAGAZINE, Dec. 18, 1989).

Cowley, *supra* note 64.

See, e.g., Cowley, *supra* note 64. For example, included in the NEWSWEEK article was the story of a 39-year-old woman who had suffered most of her life with depression and bulimia. No other treatment had relieved her suffering; however, within a month of taking

(continued...)

of the risks and benefits of Prozac, the media drew the conclusion that in spite of possible side effects, Prozac was a big improvement over older antidepressants.⁷⁶

Simultaneously, media attention began to focus on a study by Harvard Medical School physicians that created a storm of public controversy about the safety of Prozac, causing the drug to suffer increasing public disapproval. The study suggested that in rare cases, patients taking Prozac became suicidal, manic or violent.⁷⁷ The authors, psychiatrists at McLean Hospital in Belmont, Massachusetts, described six psychiatric inpatients who had received Prozac during their course of treatment at the hospital. The study said that each of the six patients developed obsessively intense thoughts of suicidal and violent behavior that abated only after discontinuation of Prozac.⁷⁸

Within months of the first media accounts of the Teicher study, Prozac suffered from public disapproval that cost Lilly, consumers, and the FDA a substantial amount. The media had picked up the story of problems associated with Prozac. Individuals, believing that Prozac had severely harmed them while they were taking it, formed a nationwide support network for all who

⁷⁵(● ..continued)

Prozac, she enthusiastically claimed to be 1,000% better, taking on things she never would have before taking the drug. *Id* Other stories reported in the media describe similar miraculous cures.

⁷⁶ Cowley, *supra* note 64.

Martin H. Teicher et al., *Emergence of Intense Suicidal Preoccupations During Fluoxetine Treatment*, 147 AM. J. PSYCHIATRY 207 (1990) [hereinafter Teicher study]. The study provided only anecdotal evidence of the experience of these six patients and did not draw the specific conclusion of a causal link between Prozac and violence.

⁷⁸ *Id* at 209.

believed they had been victimized by the drug.⁷⁹ Others filed a series of lawsuits, on their own behalf or on behalf of family members who had committed violent acts while taking Prozac, using the Teicher study as evidence of the fact that Lilly knew or should have known that Prozac was dangerous.⁸⁰ Though Dr. Teicher himself was reported as saying that his study was not conclusive,⁸¹ the alarm about the safety of Prozac began to escalate. Reports to the FDA of adverse reactions to Prozac increased astronomically,⁸² and articles began to appear throughout the nation's newspapers about the alleged link between Prozac and violent behavior. One of the popular anecdotes used to show Prozac's destructive power was the case of Joseph Wesbecker, a former press operator in Louisville, Kentucky. Wesbecker, who was being treated with Prozac, opened fire with an AK-47 at his workplace, shooting twenty of his co-workers and killing nine, including himself in September 1989.⁸³ Three widows of the eight workers killed filed suit.

Allen G. Breed, *Ex-Users of Prozac Form Support Group*, THE COURIER-J. (Louisville, Ken.), June 3, 1990, available in WESTLAW, 1990 WL 4474366.

⁸⁰ Em Marcus, *Is It Really the Wonder Drug for Depression?*, WASH. POST, Aug.

28, 1990, available in WESTLAW, 1990 WL 2112864. The article was published on August 28

and reported that more than half a dozen lawsuits had been filed in the past month, *Id.*, just

four months after Cowle's article in NEWSWEEK, *supra* note 64.

See Demitri Papolos and Janice Papolos, OVERCOMING DEPRESSION 162 (rev. ed. 1992).

Between June 3, 1990, when THE COURIER JOURNAL (Louisville, Ken.) reported

on the founding of the Prozac Survivors Support Group, see Breed, *supra* note 79, and August 3,

1990, the date the WASHINGTON POST obtained data from the FDA, see Marcus, *supra* note 80,

reports of adverse reactions had risen from 7,000 to 8,900. That increase represents an average

of 31.6 calls to the FDA each day, including weekends, during the sixty days between June 3 and

August 3.

⁸³ Marcus, *supra* note 80. The story is detailed in many of the media reports on Prozac in late 1990 and 1991 and varies slightly in some of the minor details.

against Lilly for \$50 million each in September 1990, alleging that Prozac was unsafe and dangerous.⁸⁴

Wesbecker's case attracted the attention of the Church of Scientology (the Church), a group known to be opposed to psychiatric treatment. The Church launched a vigorous campaign to discredit Prozac and ultimately became responsible for Prozac's slide from fame and fortune.⁸⁵ Their tactics included providing information and scientific data to plaintiffs suing Lilly, appearing on talk shows, and spending \$2 million on advertisements attacking Prozac.⁸⁶

As a result of all the negative publicity, Prozac's sales dropped, as did Lilly's market share of antidepressant sales for Lilly.⁸⁷ Just as they had demanded to be put on the drug, patients responded to the media battle by taking themselves off Prozac and by refusing it when their physicians recommended it⁸⁸ Patients making these decisions for themselves often did so at their

8.4 Rosenbaum, *supra* note 60, at 10.

85 Paula Span, *A Dose of Controversy*, DET. NEWS, Aug. 29, 1991, *available in* WESTLAW, 1991 WL 4661317 (reporting that the Church's attack caused most of the public furor over Prozac). For a thorough review of the Church's role in undermining public confidence in the drug, see Catherine M. Vale, *The Rise and Fall of Prozac: Products Liability Cases and The Prozac Defense in Criminal Litigation*, 12 ST. LOUIS U. PUB. L. REV. 525, 536-39 (1993).

86 Michael Tackett, *Scientologist Campaign Shakes Drug Firm*, Cm. TRIB., June 30,

1991, *available in* WESTLAW, 1991 WL 9390370. The Church's pressure was intense. Full-page advertisements in USA TODAY ran for two weeks attacking Lilly. A third week of advertisements promoted the Church and included glossy inserts critical of Lilly. *Id*

87 *Id*

88 Rosenbaum, *supra* note 60, at 10-11. As an example of this phenomenon, Dr. Rosenbaum reprinted the following letter received by a colleague:

Dear Doctor,
(continued...)

own peril⁸⁹ Eventually, Lilly responded by launching its own aggressive legal strategy to combat public relations problems, which included offers to pay all legal costs for physicians sued for malpractice after prescribing Prozac and offers to assist prosecutors by providing data and expert witnesses when criminal defendants used Prozac as a defense. 90

Throughout the controversy, the FDA maintained that Prozac was safe and effective.⁹¹ Nonetheless, under pressure from the Citizens Commission on Human Rights (CCHR), the arm of the Church dedicated to exposing psychiatric abuses, the FDA convened its

88(.. . continued)

I wish to discontinue my Prozac. I watched the Joan Rivers show yesterday and even though you had given me the paper explaining those negative things about Prozac, this program really gave me second thoughts.

I will just try harder to get myself together, to get to more Al-Anon meetings and hope for the best. I have limited medical coverage and I came to you with sincere hopes. Thank you for considering me, sorry for any inconvenience.

Id at 11. The letter shows the problem inherent in the negative publicity. Al-Anon meetings, geared toward helping alcoholics avoid the temptations of alcohol, may ameliorate this patient's symptoms but will not treat the patient's depression. Here, the author has had the hope of treatment taken away and believes that there are few options available for dealing with the problems s/be faces (I have limited medical coverage). The expense of choosing to go without treatment, however, will be either continuing to live a life of diminished quality blunted by depression or ultimately becoming one of the ten percent or more of depressed patients who commit suicide. *See infra*, note 149.

89 Deborah Shelton Pinkney, *Prozac's Pros and Cons: Suicide Experts Debate*

Merits of the Most Prescribed Antidepressant, AM. MED. NEWS 18, Apr. 27, 1992, available in WESTLAW, 1992 WL 11291950 (quoting a psychiatrist who said that several of his patients who

were doing well on Prozac discontinued it after the negative publicity, then later attempted suicide).

90 Jan Gehorsham, *Health Watch: Prozac Maker Offers to Pay Legal Costs for Doctors Sued*, ATLANTA J. & CONST., June 6, 1991, available in WESTLAW, 1991 WL 7796602.

91 Thomas M. Burton, *Medicine.' Scientologists Fail to Persuade FDA on Prozac*, WALL ST. J., Aug. 2, 1991, available in WESTLAW, 1991 WL-WSJ 597423.

Psychopharmacological Drugs Advisory Committee in September 1991, to investigate further the claims made against Prozac in particular and antidepressants in general. Following a public hearing and consideration of scientific evidence on September 20, 1991, the Committee recommended remaining on the course the FDA had been following: there should be no label changes for Prozac and there was no evidence of a link between Prozac and violent behavior.⁹² The FDA had received 14,100 reports of adverse reactions occurring in connection with Prozac since the drug's approval in 1987.⁹³ The FDA continued to defend Prozac, though, arguing that the drug's benefits outweighed its possible risks, because there were only 500 reports of suicide attempts associated with Prozac use while three million Americans had been given or were taking Prozac.⁹⁴ Absent conclusive scientific data of a causal link between Prozac and violence, the FDA maintained that the drug should be considered safe.⁹⁵ Despite such assurances, however, Prozac was clearly suffering from public disapproval, as Prozac's market share eroded because of the negative publicity.⁹⁶ Thus, not only were patients suffering from a lack of treatment, but Lilly was also expending substantial amounts to indemnify physicians and fund prosecutions, while the FDA was wasting resources on public hearings that confirmed its judgment.

⁹² Panel. 'Data Fail to Link Prozac, Suicidal Actions, Associated Press, ARIZ.

REPUBLIC/PHOENIX GAZETTE3, Sept. 21, 1991, available in WESTLAW, 1991 WL 6035394. See also, *Committee Advises FDA on Antidepressants*, 25 FDA CONSUMER 5, (Dec. 1991), available in LEXIS, News Library, Arcnws file.

Id

Committee Advises FDA on Antidepressants, *supra* note 92.

Id

⁹⁶ *Supra*, note 86. See also, Ken Kusmer, *FDA Approves New Form of Drug*, The Associated Press, Apr. 25, 1991, available in WESTLAW, 1991 WL 6183244.

B. Prozac's Rehabilitation

In early 1993, Prozac began to reclaim the public's approval with the help of Dr. Peter Kramer, an associate clinical professor of psychiatry at Brown University and private practitioner in Providence, who published *Listening to Prozac.*⁹⁷ A Psychiatrist Explores Antidepressant Drugs and the Remaking of the Self The book chronicled Dr. Kramer's experience prescribing Prozac to his patients. Dr. Kramer's description of Prozac and of its capacity to make his patients appear to be better than well⁹⁷ sparked new interest in Prozac because of its capacity to improve the personality of the person taking it. Describing this phenomenon, Dr. Kramer wrote that Prozac appeared to [give] social confidence to the habitually timid, [make] the sensitive brash, [lend] the introvert the social skills of a salesman. Prozac was transformative for patients in the way an inspirational minister or high-pressure group therapy can be....⁹⁸ The book spent three months on the New York Times bestseller list and the public's confidence in the drug rebounded⁹⁹ As proof of its rehabilitated reputation, Prozac posted a 30% increase in sales between 1992 and

1993.¹⁰⁰

Peter D. Kramer, LISTENING TO PROZAC: A PSYCHIATRIST EXPLORES ANTIDEPRESSANT DRUGS AND THE REMAKING OF THE SELF at x (1993).

⁹⁸ Id at xv.

Anastasia Toufexis, *The Personality Pill (Prozac)*, TIME, Oct. 11, 1993, available in WESTLAW, 1993 WL 2929609. Without directly tying the increased use of Prozac to the publication of Dr. Kramer's book, the article did report that there were a growing number of people using Prozac and that the drug appeared to be making a comeback. Another reporter described the book as another makeover for the drug, increasing its popularity among Americans. Susan Brink, *Singing the Prozac Blues*, U.S. NEWS & WORLD REP., Nov. 8, 1993, available in LEXIS, News Library, Arcnws file.

¹⁰⁰ Michael W. Miller, *Listening to Eli Lilly: Prozac Hysteria Has Gone Too Far*,

(continued...)

In spite of this apparent new success in the public forum, other problems continued to mount for the Prozac. The Church had not abandoned its campaign against Lilly and Prozac. The head of the CCHR published an editorial in August 1994, reviewing FDA documents obtained through the Freedom of Information Act (FOIA) and pointing out flaws in the studies performed by Lilly in support of its application for FDA approval.¹⁰¹ CCHR also continued to drive up the costs associated with the negative publicity by filing a defamation suit against a Lilly executive¹⁰² and by continuing to provide assistance to products liability plaintiff¹⁰³ and to criminal defendants.

Moreover, evidence was beginning to mount that the drug caused some serious side effects and interactions for a significant number of patients using Prozac. For example, contrary to the original marketing information, as many as 34% of those taking Prozac experienced sexual dysfunction.¹⁰³ Others experienced personality changes while taking Prozac,¹⁰⁴ and physicians

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WALL ST. J., Mar. 31, 1994, *available in* WESTLAW, 1994 WL-WSJ 298534.

101 Richard Warner, *Dangers of Miracle Cure Should be Heeded*, SEATTLE POSTINTELLIGENCER, Aug. 9, 1994, *available in* WESTLAW, 1994 WL 612 0737. Warner revealed information contained in FDA documents that had limited the FDA judgments about safety and efficacy, including a warning that Prozac's side effect profile might worsen patients' depression and a note on the review of clinical data that leads to the conclusion that the true adverse effects of Prozac were not known at the time of marketing. *See infra*, notes 130-174 and accompanying text (analyzing the FDA approval process for Prozac). That analysis will show that Warner's information was correct.

102 *Business Ledger*, NEWSDAY 41, Feb. 5, 1992, *available in* WESTLAW, 1992 WL

77237 15 (reporting that the Church filed a \$20 million suit against Mitchell Daniels, a senior executive of Eli Lilly & Co.,... [alleging that] 'Daniels attempted to discredit and malign the church as a source of the protest against Prozac by making false and defamatory statements' about the church).

103 Frederick M. Jacobsen, *Fluoxetine-Induced Sexual Dysfunction and an Open Trial of Yohimbine*, 53 J. CLIN. PSYCHIATRY 119 (1992). The original marketing information

(continued...)

were becoming increasingly aware of dangerous interactions with other drugs.¹⁰⁵ Most of these effects had been under-reported or overlooked when the drug was first marketed.’¹⁰⁶

One serious side effect that began to be reported was the serotonin syndrome. Though known to occur in some patients using antidepressants, the serotonin syndrome was becoming more common as the use of SSRIs was becoming more widespread.¹⁰⁷ Serotonin syndrome is a toxic reaction that produces a cluster of serious conditions, including (1) altered mental status, which is reflected in symptoms such as confusion, mania and agitation, (2) autonomic dysfunction, which is reflected in symptoms such as blood pressure fluctuation, diarrhea, hyperthermia and shivering, and (3) neuromuscular abnormalities, whose symptoms include restlessness, incoordination, rigidity, seizures and tremor.¹⁰⁸ Though experts do not completely understand its cause, it is generally believed that the buildup of serotonin in the system, which develops as the

103(..continued)

found that only 1.9% of clinical test subjects using fluoxetine suffered from sexual dysfunction while using the drug. FOOD AND DRUG ADMINISTRATION, SUMMARY BASIS OF APPROVAL FOR NDA, 18-936, Prozac (Fluoxetine Hydrochloride) 35 (Oct. 3, 1988) [hereinafter, SBA]. The problem with this information is that sexual dysfunction can lead to noncompliance with drug therapy. *Id* at 119. This makes treating the patient’s depression much more difficult, unless the physician is aware of the possibility that this adverse effect will occur and can help the patient cope with the difficulty. Physicians would not necessarily focus on Prozac use as a source of sexual dysfunction when the marketing information estimated its incidence at such a low rate.

This was first documented in Kramer, *supra* note 97 (describing many of his patients who underwent personality changes after beginning to use Prozac).

¹⁰⁵ Brink, *supra* note 99. *See, e.g., infra*, note 110 and accompanying text.

¹⁰⁶ *Id See also*, Jacobsen, *supra* note 103, at 119.

¹⁰⁷ Thomas G. Martin, *Serotonin Syndrome*, 28 ANNALS OF EMERGENCY MED. 520, 524 (1996).

¹⁰⁸ *Id* at 52 1-22.

SSRI prevents the depletion of serotonin in the brain cells, becomes excessive and causes some or all of these conditions to develop in patients who already have sufficient serotonin in their brains.’¹⁰⁹ The reaction can often be managed by discontinuing the use of the drug, but it can result in death, particularly when the use of an SSRI occurs in conjunction with the patient’s taking other medications.⁰

The specter of suicide and violence had also not disappeared. In Texas, consumer advocates began to seek state remedies to require the labeling information that the FDA would not authorize.’ In the United Kingdom (UK), a review of Prozac and other SSRIs was being published, which tended to show an indirect link between SSRIs and suicide. The physician serving as the secretary of the British Association for Psychopharmacology concluded that ‘There is now sufficient documentation to sustain the argument that Prozac may lead to the emergence of suicidal ideation,² and the common adverse effects attributed to Prozac, such as agitation,

~ *Id*

¹¹⁰ *Id* at 520-21.

Mark Smith, *Prozac Targeted by Health Group/Warning Label Called For*, HOUS. CHRON., Jan. 1, 1994, *available in* WESTLAW, 1994 WL 4592054 (reporting that the Texas Mental Health Consumers had petitioned the Texas Department of Health to require pharmacists to place labels on Prozac bottles warning of the possibility that Prozac could cause patients to become suicidal and aggressive, because patients did not receive adequate warning about the adverse effects associated with Prozac from either their physicians or the prescription bottle itself). By petitioning to require pharmacists to attach labels to bottles used in dispensing the prescription, the group would skirt the issue of federal pre-emption over prescription drug labeling, because the practice of pharmacy is regulated by state law.

¹¹² Christine Doyle, *The Cloud over Bottled Sunshine*, DAILY TELEGRAPH (London), Mar. 1, 1994, *available in* WESTLAW, 1994 WL 11340497 (quoting an article that would be published later in the year) (internal quotation marks omitted).

nervousness, restlessness and panic, might foster bizarre thinking in predisposed people.³ Because physicians relied heavily on the FDA's judgment that Prozac was safe and

effective, two trends had developed in the prescribing of Prozac: (1) increasing numbers of patients were using the drug, even though many of them did not meet the diagnostic criteria for depression, and (2) physicians began to leave their patients on Prozac indefinitely. Misdiagnosis appeared to be the primary reason for the increase in the use of Prozac, a phenomenon that developed because of the increase in the number of nonspecialists prescribing Prozac.⁵ Moreover, with Prozac's more favorable side effect profile, physicians were more comfortable leaving their patients on Prozac indefinitely,⁶ ignoring the fact that Prozac's long-term risks were unknown because of the lack of long-term testing.

These trends were problematic because of the developing evidence on side effects, primarily the potentially fatal serotonin syndrome. By prescribing Prozac to patients who really did not need it and by leaving patients on the drug indefinitely, physicians exposed their patients to the risk that their brains would build up too much serotonin and they would, essentially, overdose on serotonin. Also, studies began to show that Prozac carried with it the same failure

Id (internal quotation marks omitted).

³ Natalie Angier, *Doubts Over the New Antidepressants*, ATLANTA J. & CoNST., Dec. 27, 1993, available in WESTLAW, 1993 WL 4018418.

⁵ Brink, *supra* note 99. The article cited a study that found that 63% of prescriptions for antidepressants were made by a nonspecialist, and more than half of those prescribing physicians spent three minutes or less with the depressed patient discussing the disorder. Nonspecialists in this situation fail to determine if all the symptoms that should be present before drug therapy is started are present for the patient about to receive the prescription.

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Angier, *supra* note 114.

rate as the older antidepressants, meaning that it was not the miracle cure that it had originally been reported to be;⁷ thus, without proper diagnosis and treatment, patients actually experiencing depression continued to suffer. As a result, consumers would continue to provide mixed signals regarding their acceptance of Prozac, because there now were legitimate dangers associated with it. In promoting these trends, physicians ignored the effect that the public has on the approval and marketing process and helped to increase the costs associated with the controversy.

Lilly's response to all the new information was mixed. On the one hand, Lilly defended Prozac against the data collected on sexual dysfunction, saying that sex difficulties will almost always be under-reported in clinical trials; challenged accounts such as Dr. Kramer's, saying that personality changes naturally result from depression and the effect is not unusual; and, defended itself against the charge that it had failed to detect some drug interactions, arguing that no company can test all the possible drug interactions that are dangerous.¹⁸ Much of this is true, because clinical trials cannot possibly uncover all the information about the adverse effects associated with a new drug.⁹ Prozac's success had made it profitable enough to pursue FDA approval for labeling the drug as a treatment for other illnesses, and eventually Lilly would receive approval to market the drug as safe and effective not only for the treatment of depression but also

~ Angier, *supra* note 114.

118 Brink, *supra* note 99.

~ See *infra*, note 226 and accompanying text. It also seems likely that any study of a drug will tend to underestimate the incidence of sexual dysfunction because of the delicacy of exploring the issue with clinical test subjects.

for the treatment of obsessive-compulsive disorder.¹²⁰

On the other hand, Lilly appeared to be rethinking its strategy with Prozac, launching an advertising campaign that appeared to discourage the use of Prozac. The advertising campaign had as its goal to deplore the media's role in exaggerating the drug's power and making light of depression.¹²¹ The *Wall Street Journal* characterized the motivation behind this unusual strategy as being born of concern that Prozac's over-use was trivializing mental illness, discouraging those truly depressed from seeking treatment and making it difficult to have mental health treatment included in the national health plan being considered at that time.¹²² Lilly's motivation could also have stemmed from a desire to limit its exposure to potential liability and to improve its image, which the controversy had severely damaged. While it would be difficult if not impossible to verify empirically that in fact the nation was beginning to trivialize the issue of mental illness, and regardless of Lilly's true motives, Lilly raised a good point. If the over-use of Prozac could lead to the under-treatment of mental illness, then the social costs would be enormous¹²³ and Prozac

120 See PHYSICIANS' DESK REFERENCE 935, 936 (51st ed. 1997). Once a drug has been approved for marketing, the sponsor may only market the drug for the indication listed on the original NDA. To market the same drug for use in treating other illnesses, the sponsor must obtain an approval from the FDA, indicating that the drug is safe and effective for the treatment of the other condition or conditions. See Walsh and Pyrich, *supra* note 1, at 943-45 (outlining the process for obtaining approval for a supplemental indication and concluding that because of the cost in both time and money involved, manufacturers are reluctant to submit [applications for supplemental approval] for their products).

121 Miller, *supra* note 100.

122 *Id.*

123 The costs of depression are difficult to estimate but are clearly quite high. The social cost of depression may be as high as \$40 billion annually in lost productivity, lost income, and health-care costs. David B. Cohen, OUT OF THE BLUE: DEPRESSION AND HUMAN NATURE
(continued...)

would not be serving the purpose it was intended to serve, namely to provide a safer means of treating patients with a devastating illness.’²

Although the intensity of the controversy has now subsided, the public’s perception of Prozac is mixed. While many products liability plaintiffi complain that Prozac is unsafe and is responsible for causing severe adverse effects in certain users,¹²⁵ the use of Prozac and the related SSRIs continues to rise. In March 1996, Lilly’s sales of Prozac began to slow down, with Lilly posting only a six percent increase in new prescriptions,¹²⁶ and Prozac has struggled to maintain its market share against the newer SSRIs coming onto the market.¹²⁷ Prozac has continued to do well, though, with its dollar sales up 14% at the end of 1996 to \$2.3 billion.¹²⁸

This history compels the conclusion that the controversy over Prozac’s safety drained the

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52 (1994). The personal cost for the depressed individual and his or her family would be difficult to measure, though an important indicator is the more than 15 percent of depressed people who commit suicide and the more who come close. *Id* at 51. For a moving account of the personal and social costs of depression, see *id* at 50-2.

124 *See infra*, notes 133-136 and accompanying text (reviewing the data showing Prozac to have certain safety advantages).

125 Plaintiffs continue to pursue products liability lawsuits against Lilly. *See, e.g., Winider et al. V. Eli Lilly and Company*, 101 F.3d 1196 (1996) (noting that seventy-five Prozac cases have been consolidated by the Federal Judicial Panel on Multidistrict Litigation into a class action suit against Lilly). Currently, though, no judgments have been entered against Lilly and the litigation continues to make its way through procedural issues.

126 Trade & Gov’t Memos, F-D-C REP. (‘The Pink Sheet), May 27, 1996, *available in* LEXIS, Health Library, FDC file.

127 Trade & Gov’t Memos, F-D-C REP. (‘The Pink Sheet), Jan. 13, 1997, *available in* LEXIS, Health Library, FDC file.

128 *Id*

public coffers and imposed a huge tax, financially and socially, on society, because the regulatory process for drug approval did not account for the fact that the public would operate its own process as a check on the FDA. Products liability suits placed an additional tax on the company who, in good faith, had already expended vast resources to provide a drug to the public that the public, through its political process, had judged to be beneficial in the treatment of depression. The politically accountable agency charged with making the public's decisions expended additional resources against the challenge to its expertise and to its considered judgment that the drug would be beneficial, and physicians were taxed with malpractice suits for relying on this agency's findings. The greatest cost came in the losses sustained as patients in need of treatment did not receive, either because of their fear of the drug induced by negative hype or because hysteria had trivialized their illness, a safe medication that could be effective for them.¹²⁹ Any effort, then, to reform the drug approval process must consider these effects on the public, the FDA, drug manufacturers, and the healthcare professionals who rely on the FDA's judgment, because streamlining approval has the potential to create similar controversies that, if not more severe than that associated with Prozac, may become more frequent and are likely to be just as costly.

C. The **Drug** Approval Process for Prozac

Reviewing the process that Prozac underwent to obtain FDA approval for marketing shows that the process was deficient in several respects. There was actually a low threshold for proving efficacy, some of the tests conducted were unnecessary, and little was really understood

¹²⁹ See *supra*, note 123 (estimating the costs of depression at \$40 billion annually).

about the effects associated with fluoxetine use at the time the drug went on the market.¹³⁰ As a summary matter, the SBA indicates that the studies conducted on fluoxetine were

sufficient to meet the statutory requirements of demonstrating that the drug was both safe and effective in the treatment of depression, though safety and effectiveness of use for longer than six weeks was not established.¹³¹ The initial recommended dose was 20mg, with dose increases recommended after several weeks of no improvement.¹³²

1. Establishing Safety

Both preclinical and clinical testing established that fluoxetine administration had no immediate safety problems; however, this conclusion about fluoxetine's safety was limited, for there were no conclusive data on the safety of long-term use nor was there a definitive conclusion about the effect that fluoxetine's unique cluster of adverse effects (side effect profile) would have on the overall safety of the drug for large populations of patients. Preclinical animal testing was useful in allowing the FDA to conclude that fluoxetine's major benefit compelling approval of the drug was its safety in high doses, making it very difficult for patients using fluoxetine to

130 After approving a new drug, the FDA issues a Summary Basis of Approval (SBA), which provides a review of the documentation supporting the drug's approval. This section examines the SBA for fluoxetine, and is limited by the data contained therein.

SBA, *supra* note 103, at I.

132 SBA, *supra* note 103, at 2. The SBA notes that therapy for depression can require treatment for longer than four weeks, as acute episodes of depression normally respond only after several months of treatment. *Id.* Antidepressant treatment for months-long periods of time is generally accepted as a standard treatment regimen for depression. See Pedro L. Delgado and Alan J. Gelenberg, *Decision Making in the Use of Antidepressants*, *Treatment Considerations*, in THE HATHERLEIGH GUIDE TO MANAGING DEPRESSION 265 (Joya Lonsdale, ed. 1996). At the end of three to four weeks, antidepressants will usually have had some effect on the patient, but the patient will generally not experience the full therapeutic effect of an antidepressant until week twelve of the drug therapy. *Id.* at 273.

commit suicide.¹³³ Most of the animals tested showed that high doses of fluoxetine produced convulsions and tests on dogs revealed a moderately decreased heart rate.¹³⁴ Studies on cats showed that there were no cardiovascular effects associated with fluoxetine use, such as blood pressure changes, cardiac contractility or cardiac conduction.¹³⁵ These data were particularly relevant to the conclusion that fluoxetine overdose was unlikely to lead to death.¹³⁶ Finally, preclinical testing established the potential for a dangerous interaction with MAO-inhibitors.¹³⁷

The clinical data supported the conclusions about the safety of fluoxetine, particularly the safety of fluoxetine in overdose, and, contrary to the public judgment that fluoxetine was dangerous, the FDA found no clear evidence for any clinically significant safety risk associated with the use of fluoxetine.¹³⁸ Phase I clinical studies showed no safety problems with

¹³³ Richard Kapit, *Safety Review of NDA 18-936*, SBA, *supra* note 103, at 2 (concluding that fluoxetine does not appear to cause serious toxicity. . . . If significant amelioration of depression is a demonstrable [sic] effect of this drug, this benefit would appear to outweigh any potential risks associated with its clinical use which became evident among patients exposed to fluoxetine reported in this NDA). *See infra*, note 149 (explaining the importance of this finding of safety in overdose as it relates to depressed patients).

¹³⁴ SBA, *supra* note 103, at 17.

¹³⁵ *Id.* at 5-6.

¹³⁶ Rosenbaum, *supra* note 60, at 10.

¹³⁷ SBA, *supra* note 103, at 16. MAO-inhibitors are antidepressants that are frequently associated with dangerous interactions with certain foods and medications. Steven Zavodnick, *Somatic Therapies of Depression*, in *DEPRESSIVE DISORDERS: FACTS, THEORIES AND TREATMENT METHODS* 275, 281-84 (Benjamin B. Wolman and George Stricker eds., 1990). The list of substances to avoid ranges from alcohol, cheese, certain meats, and beans to cold and allergy medicines, appetite suppressants, and other antidepressants. *Id.* at 284. Thus, a determination of possible interaction with MAO-inhibitors was critical to the finding of safety.

¹³⁸ *Id.* *supra* note 133, at 12.

fluoxetine.³⁹ Furthermore, the sponsor pooled and evaluated the safety data⁴⁰ from all clinical trials, from which the FDA concluded that there were no clinically significant changes in hematology, chemistry or urinalysis parameters, blood pressure or heart rate changes, or liver functions associated with fluoxetine use.” The drug was associated with decreased weight, but that side effect was determined not to be sufficiently dangerous.⁴² At most, there were some changes in blood hemoglobin and LDH levels that could be dangerous if not monitored carefully.⁴³

Although both preclinical and clinical data established the finding of safety in overdose⁴⁴ and the safety of use in short-term situations, there were very little data on the long-term use of fluoxetine, which made it impossible to draw conclusions about the drug’s safety during long-term use.⁴⁵ The data on adverse effects associated with fluoxetine use was reviewed by combining

~ Kapit, *supra* note 133, at 7. Only one Phase I test subject had a serious effect – a ~mild seizure – while on fluoxetine, but no conclusions were drawn from this report. *Id*

140 The pooled population of fluoxetine-exposed test subjects had 6,070 patients. *See* SBA, *supra* note 103, at 27.

SBA, *supra* note 103, at 32.

142 Kapit, *supra* note 133, at 12.

143 *Id* at 11-12.

’ While 38 clinical test subjects attempted overdoses with fluoxetine, only two overdoses resulted in death, and those patients had combined extremely high doses of fluoxetine (1,800mg and 3,000mg) with other drugs at the time of overdose. SBA, *supra* note 103, at 38. The other 36 patients recovered without any lasting effects. *Id*

’s The FDA acknowledges that an approval process that focuses on pre-market testing and proof will always be limited in the data that can be collected. Thus, it is never the case that a drug has received a thorough review of the long-term effects associated with continuous use. *See infra*, note 226 and accompanying text.

clinical data on 1,427 patients who received fluoxetine. Of these patients, only 211 had received fluoxetine for more than 183 days and only 74 of the 211 had received fluoxetine for more than 365 days.⁶

These limited findings present problems, because at the time of this testing, experts generally believed that antidepressant therapy required treatment for several months.⁷ Thus, the safety data was not sufficient to determine that administering fluoxetine to human patients would be safe under the conditions that most patients would use the drug, as the serotonin syndrome showed.⁸ The time required to conduct the necessary tests, however, would delay the drug's entry onto the market, thereby depriving physicians and patients of a treatment that had significant safety advantages over drug treatments then available. Because physicians could prescribe fluoxetine to their depressed patients without fear that the drug would accomplish a suicide attempt, as was true with older antidepressants, delaying the availability of fluoxetine could compromise the safety of patients already receiving antidepressant drug therapy.⁹

¹⁴⁶ *Review and Evaluation of Clinical Data: Original NDA Submission*, SBA, *supra* note 103, at 121 [hereinafter *Original NDA Submission*]. Of the 6,070 test subjects in the pooled safety sample, only six percent of the population had received the drug for more than one year.

¹⁴⁷ *See, e.g.*, SBA, *supra* note 103, at 2 (The full antidepressant effect may be delayed until 4 weeks of treatment or longer... . It is generally agreed among expert psychopharmacologists (circa 1987) that acute episodes of depression require several months or longer of sustained pharmacologic therapy). *See also, supra*, note 132.

¹⁴⁸ *Supra*, notes 107-110 and accompanying text.

The potential for suicide in depressed patients is great: as many as ten percent of patients with major depressive disorder will succeed in committing suicide unless they are treated effectively. Alan A. Stone, Psychiatry and the Law Classroom Presentation at Harvard Law School, January 21, 1997. *See also* Cohen, *supra* note 123, at 51(1994) (placing the percentage of depressed patients who commit suicide at more than 15%). Thus, any medication that will

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Moreover, the conclusion of fluoxetine's safety was tainted by the procedure used to determine the adverse effects associated with fluoxetine use. Because Lilly had given no indication of the methods used to collect the data on adverse effects, the clinical data review concluded that there was no systematic procedure in place and that the reporting of adverse effects was left to the discretion of the clinical investigators; in addition, Lilly instructed investigators not to include experiences caused by depression.¹⁵⁰ The lack of a systematic procedure, combined with the specific instruction not to note depressive symptoms,

may have altered the relative frequencies of many adverse experiences. Each investigator would have had his own idea of what depressive experiences might comprise resulting in a lack of generalizeability [sic] from one investigator to the next. Not surprisingly, many antidepressants (and anxiolytic) agents do produce adverse effects which are known to be symptoms of depressions, (e.g., insomnia [sic], nausea, anxiety, tension, restlessness) leading to a possible underrepresentation of these effects.¹⁵¹

Thus, any information on adverse experiences provided postmarketing was, at best, incomplete and, at worst, irrelevant or misleading. Though the FDA obviously concluded that the

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result in death if used in a suicide attempt poses serious ethical problems for the prescriber. The considerations given to safety in reviewing fluoxetine were therefore not irrational, and it could be justifiable for the FDA to conclude that this significant advantage outweighed the risks of having incomplete long-term data. However, there are no data that establish how often the older antidepressants were used to attempt suicide, making it unclear whether this advantage of fluoxetine outweighed the risk of rushing the drug to market based on clinical test data derived from trials of inadequate duration.

¹⁵⁰ *Original NDA Submission*, *supra* note 146, at 122. Besides spontaneous reporting, Lilly could have instructed researchers to conduct systematic interviews designed to elicit adverse effect reports. Instead, Lilly instructed investigators to record all patient experiences on the drug and to make a determination as to the causation of the experience. Lilly provided no parameters or criteria for making that determination. *Id*

¹⁵¹ *Id*

information was sufficient to allow a basic understanding of the adverse effects associated with fluoxetine use, the FDA should have required Lilly to complete and correct this information upon marketing so that physicians and patients would have more accurate information. The FDA's statutory responsibility after approval extends only to removing drugs that are found to be an imminent hazard,⁵² and the FDA has consistently interpreted the authority to withdraw hazardous drugs from the market as giving it the authority to conduct post-marketing surveillance of drugs. Thus, if the FDA will incur this responsibility, then the FDA also has the responsibility to ensure that information on adverse effects is as complete as possible.

With such skewed information on the adverse effects associated with fluoxetine, there was no clear indication of what the adverse effects of fluoxetine use were likely to be. Considered with the advantage of hindsight, this aspect of the approval process is troubling. Clinical investigators, confronted with patients reporting symptoms such as those reported in the media after marketing (including worsening depressive symptoms and suicidal ideation),⁵³ would have been justified in leaving out this information from their reports on the basis of the instructions Lilly provided. Thus, Lilly's assertions during the controversy that suicidal ideation and other violent tendencies were not adverse effects of fluoxetine use were misleading, for in fact there was no good evidence either in support of or opposed to this assertion.

Moreover, there was apparently never any attempt to make a precise determination of the effect that fluoxetine's new side effect profile would have on the patients taking it. The limited

152 21 U.S.C.A. § 355(c) (West Supp. 1973-1995). *See also, supra* part 11.C. (discussing postmarketing regulation by the FDA).

⁵³ *See supra*, part [II].

data on adverse effects had established that fluoxetine use was associated with a significantly different cluster of side effects from older antidepressants, which had the potential to make depressed patients worse. Unlike older antidepressants, which had a very different side effect profile, fluoxetine tended to produce side effects that are often associated with depression, such as nausea, insomnia, nervousness, anorexia and weight loss.¹⁵ All of the clinical studies revealed that these symptoms were the most frequently reported of the side effects, and the review of the safety data concluded that 'These adverse effects of fluoxetine treatment may negatively affect patients with depression. . . . It is possible that fluoxetine treatment might, at least temporarily, make their illness worse.'¹⁵⁵ At the time of the safety review, it was unclear how great a risk this new side effect profile would be. Dr. Kapit concluded that the severity of the risk did not appear

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great, yet he less recommended that the labeling note the lack of experience with this type of profile in treating depressed patients and that postmarketing studies be conducted to

determine the severity of the risk. The SBA reports, however, only that Lilly agreed to conduct postmarketing studies in order to provide two additional efficacy studies and to assist in developing more precise directions for using fluoxetine. ~

Thus, the data collected on safety were clearly deficient in several respects. First, Lilly had not provided and the FDA had not received substantial evidence that the drug was safe for long-term use. While collecting the long-term data would be difficult without lengthening overall

's Kapit, *supra* note 133, at 11.

'~ *Id* at 15.

156 *Id*

~ SBA, *supra* note 103, at 47.

drug development time, this aspect of the safety data is troubling because most patients would use the drug for longer than four to six weeks. Second, Lilly could not tell what the adverse effects of fluoxetine use would be and the FDA made no effort to require that information. This failure was an abdication of the FDA's responsibility. Finally, neither Lilly nor the FDA attempted to determine the effects fluoxetine's side effects would have on depressed patients. Patients taking Prozac were thus at risk of becoming more depressed while not necessarily being aware that their treatment was the cause.

2. Establishing Efficacy

The data establishing efficacy also was deficient, relying on marginal findings of efficacy and requiring unnecessary tests. Though the FDA concluded that Lilly had provided three adequate and well-controlled studies sufficient to establish fluoxetine's efficacy for depression, the threshold of proof was low, establishing, at best, only a reasonable indication that fluoxetine was effective. Of the studies used to establish efficacy, the FDA concluded that one (Protocol 62) was flawed and the other two (Protocols 19 and 27) were limited in the results that were found. In the only convincing study of efficacy, Protocol 27, a six week test of fluoxetine, placebo and imipramine,¹⁵⁸ found that fluoxetine was more effective than placebo but not necessarily more effective than imipramine.¹⁵⁹ In Protocol 19, a five week comparison of fluoxetine and placebo, only a small group of patients completed the study, making its results difficult to interpret. Eleven patients on fluoxetine completed the study and thirteen patients receiving the placebo completed the study. To make a determination about the efficacy of fluoxetine, all patients who had received

¹⁵⁸ Imipramine is a tricyclic antidepressant.
¹⁵⁹ SBA, *supra* note 103, at 23.

at least a baseline measure of depression and one rating of depression while on the treatment were compared. While the FDA concluded that fluoxetine patients improved more than patients on placebo,¹⁶⁰ this finding was limited to three of the six variables used to measure efficacy.¹⁶¹ In Protocol 62, a six week comparison of fixed doses of fluoxetine¹⁶² and placebo showed that only the 20mg dose appeared to be effective. In reviewing Protocol 62, however, the reviewer noted that the data from this study could not be conclusively said to establish the effectiveness of a particular dose.¹⁶³ Another reviewer agreed that the data were hard to interpret but that their positive findings did provide evidence of antidepressant efficacy.¹⁶⁴ That conclusion, however, did not account for all the other findings that showed fluoxetine to be no different than placebo or other active drugs.

¹⁶⁰ *Id* at 20.

¹⁶¹ *Original NDA Submission*, *supra* note 146, at 59. Scores on six tests of depression were charted each week for patients in the clinical trials. The tests measured the severity of the patient's depression and improvement in the scores from week to week indicated therapeutic effect.

¹⁶² The doses were fixed at 20mg, 40mg, and 60mg.

¹⁶³ J~ Hillary Lee, *Review and Evaluation of Clinical Data: Clinical Data Amendment*, SBA, *supra* note 103, at 12. The data suggested that 20mg doses of fluoxetine were efficacious, while the higher doses, particularly the 60mg dose, were not. The design of the study was flawed because those patients assigned to the 60mg group had not been titrated to that dose; that is, they had not gradually been brought up to that dose. (Titration is a standard procedure that allows the body to adjust gradually to a high dose and thus minimizes adverse experiences.) As a result of the lack of titration, more 60mg patients dropped out of the study earlier because of uncomfortable adverse effects, yet the data for these patients was compared with the data of patients completing the entire six week study. That comparison confounded the statistical analyses of the data and the reviewer concluded that this confounding meant that it may not be appropriate to conclude that low doses are better than high. *Id*

¹⁶⁴ Thomas P. Laughren, *Handwritten Note*, attached to Lee, *supra* note 163, at 13.

The clinical data on efficacy had several shortcomings. First, the review of the clinical data noted that the placebo-controlled studies, those studies comparing fluoxetine with an inert pill, were greatly affected by dropouts. Those who were doing poorly during the first few weeks of the clinical trials could be dropped from the study and a determination made as to the drug they were taking. The review concluded that this could have affected the placebo-controlled studies because breaking a double-blind study can influence the investigator's behavior and the ability to break the double-blind may have acted as an incentive to drop patients earlier than they might otherwise have been dropped.¹⁶⁵ This, however, will always be a problem with placebo-controlled studies.¹⁶⁶ Physicians would have a strong disincentive to participate in clinical trials if they could not make a determination that a patient was responding poorly enough to merit breaking the double-blind design. Also, the patient samples were cleaned up to include only those patients with a less severe form of depression, who had the ability to communicate adequately with the

¹⁶⁵ *Original NDA Submission, supra* note 146, at 68.

¹⁶⁶ Some have debated the ethics of using placebos in clinical trials because their use deprives suffering patients from treatment that could be effective. Kenneth J. Rothman and Karin

B. Michels, *The Continuing Unethical Use of Placebo Controls*, 331 NEW ENG. J. MED. 394 (1994). These authors argue that the Declaration of Helsinki, a code of conduct for human experimentation *in* medical studies, proscribes the use of a placebo as control when a 'proven' therapeutic method exists. *Id* at 394. They would have the FDA effectively prohibit the unethical use of placebos in drug trials by requiring a persuasive ethical justification whenever placebos are used. *Id* at 397. Otherwise, the drug company would have to use standard drug treatments as controls in clinical trials. Had this been the case with fluoxetine, there would not have been two adequate and well- (that is, standard drug-) controlled studies that could have supported approval. *See* Lee, *supra* note 163, at 79-102 (reviewing the active drug controlled studies and determining that Protocols 20 and 23 – the only two studies that showed fluoxetine to be superior to the active control drug – suffered from flaws in design).

investigators, and who were not taking other medications.¹⁶⁷

The animal studies conducted to establish the therapeutic potential of fluoxetine were unconvincing and, unlike the animal studies used to demonstrate fluoxetine's safety,¹⁶⁸ not useful. In the only reference to preclinical evaluations of potential efficacy, fluoxetine was shown to [antagonize] reserpine-induced hypothermia in mice.¹⁶⁹ Reserpine-induced depression, however, has limited value as a model for human depression, because it does not necessarily reflect the etiology or course of naturally-induced depression in humans.¹⁷⁰ At best, then, the studies showing that fluoxetine did act on this condition hinted at the possibility that fluoxetine might be useful in treating some forms of human depression, but only a form of depression that a small subset of depressed patients would develop. More likely the testing was superfluous; the information gathered was helpful rather than necessary or compelling, serving primarily to drive up the cost of fluoxetine's development.

¹⁶⁷ This limitation is inherent in clinical trials. *See infra*, note 226 and accompanying text.

¹⁶⁸ *See supra*, notes 133-136 and accompanying text.

¹⁶⁹ SBA, *supra* note 103, at 5. Reserpine is a drug used to treat high blood pressure that has been found to induce depressive symptoms in humans and animals alike. By administering reserpine to animals, thereby inducing a chemical depression in the animals, researchers could then determine whether or not fluoxetine would act to combat the depressive symptoms. *See* R Francis Schlemmer, Jr. et al., *Pharmacological Probes in Primate Social Behavior*, in ANIMAL MODELS OF DEPRESSION 239, 239-40 (George F. Koob et al. eds., 1989). The link between alleviation of reserpine-induced depression and the administration of fluoxetine was apparently sufficient to meet the regulatory requirement that animal studies show some evidence of efficacy before an [NI] is approved.

¹⁷⁰ *See* Gaylord D. Ellison, *Animal Models of Psychopathology: Studies in Naturalistic Colony Environments*, in PSYCHOPATHOLOGY IN ANIMALS: RESEARCH AND CLINICAL IMPLICATIONS 81, 86-90 (J.D. Keehn ed., 1979).

Of more value may have been predlinical testing that established that fluoxetine blocked the uptake of serotonin in the neuronal synapses and acted selectively on serotonin.⁷¹ Because serotonin is thought to be linked with depression, these data should have suggested by inference that fluoxetine had therapeutic potential. However, this information appears to have been used primarily to establish the pharmacokinetics of fluoxetine, for no such inference was drawn.

While the data on efficacy are underwhelming in the slight degree to which they establish that fluoxetine is effective as an antidepressant, Lilly had probably met the statutory requirement of providing substantial evidence of efficacy.⁷² In weighing the risks and benefits of fluoxetine, though, proof of efficacy probably played a smaller role in the risk-benefit calculus than the proof of safety. What tended to make fluoxetine attractive and sufficiently beneficial to warrant approval was its overwhelming evidence of safety under normal conditions of use.⁷³ In leveling the charge against the FDA and Lilly that there was not sufficient evidence that the drug was effective,⁷⁴ what the publicity tended to ignore or failed to understand was that a risk-benefit analysis of the drug was indeed favorable, justifying approval.

SBA, *supra* note 103, at 4. The availability of serotonin in the brain is believed to be a critical component in treating depression. Two studies in the late 1960s laid the foundation for believing there was a link between serotonin and depression. Henry R Boume et al, *Noradrenaline, 5-hydroxytryptamine and 5-hydroxyindoleacetic Acid in Hind-Brains of Suicidal Patients*, 2 LANCET 805 (1968); Solomon H. Snyder and Joseph T. Coyle, *Regional Differences in [3H]-norepinephrine and [3H]-dopamine Uptake into Rat Brain Homogenates*, 165 J. PHARMACOLOGY AND EXP. THERAPEUTICS 78(1969).

172 See *supra*, note 33.

173 See *supra*, notes 133-136 and accompanying text.

174 See, e.g., Warner, *supra* note 101.

IV. The Debate over Reform of the **FDA**

A. Background

Concern that the American public is being deprived of valuable drug treatments because of drug lag⁷⁵ has focused the attention on reform. Noting this drug lag, critics of the FDA argue that the 1962 Kefauver-Harris Amendments, which required proof of both safety and efficacy prior to marketing, led to more time-consuming and stringent testing requirements. Adhering to these requirements, set by a monolithic regulatory entity with too much authority and too few incentives to act efficiently, has caused the drug lag.⁷⁶

The catalyst in the debate on reform has been the AIDS crisis.⁷ America's experience with ALI(S) has provided the moral imperative to reform the drug approval process, because the process is seen as responsible for unconscionably long periods of time in which these patients must suffer without treatment. By refusing to alter the process, critics argue that the FDA condemns AIDS victims to death and allows them to suffer needlessly while waiting for

⁷ Drug lag has been defined as a gap in new drug introduction... between the

United States and other sophisticated, drug-producing and consuming nations. Rosemary Pierce

Wall, Note, *International Trends in New Drug Approval Regulation: The Impact on*

Pharmaceutical Innovation, 10 RUTGERS COMPUTER & TECH. L.J. 317, 318(1984). The

frequent refrain is that other countries have access to beneficial drug treatments long before the

FDA approves those treatments for marketing in the US.

¹⁷⁶ *Id* Although most critics have blamed drug lag on the FDA's rigorous premarketing approval requirements, some argue that the problem stems from forces other than regulation. *See id.* at 3 18-19.

⁷⁷ *See* Relihan, *supra* note 1, at 231 ('The AIDS crisis has forced the United States 'drug lag' into the public eye and has provoked a reexamination of drug testing and approval policies); Walsh and Pyrich, *supra* note 1, at 949 in response to criticisms of delays in approving AIDS drugs, the issue of 'drug lag' has begun to be addressed seriously by the FDA).

treatments to be proved safe and effective.¹⁷⁸ AIDS activists have put extreme pressure on the FDA to remedy the drug lag, whether by shortening the approval process to get treatments on the market faster or by allowing patients to import drugs from countries that will sell them. In an uncommon pairing, conservative organizations and a Republican Congress interested in decreasing the government's intervention in the free market have joined these reformers in their efforts. With new Congressional leadership in 1994, Congress placed various statutory reforms on the table and began slashing FDA funds,¹⁷⁹ while conservative think-tanks poured their resources into advocating for reform.¹⁸⁰

The FDA is not without its supporters, however, who believe that the FDA is a necessary regulatory agency with a justifiably strict paternalistic philosophy that saves lives.¹⁸¹ They advocate maintaining the present system on the grounds that the drug industry's disincentive to provide accurate information about their products creates the need for strict governmental regulation.¹⁸² Moreover, the system's focus on stringent scientific standards of proof is the only way to determine whether or not a drug is safe and effective and, absent such a determination, the

178 Relihan, *supra* note 1, at 233.

179 See, Price, *supra* note 1, at 659 (explaining the 1996 budget cuts and the political machinations involved in having the cuts restored to the budget).

180 *US Far-Right Groups Target the FDA*, MARKETLEITER, Feb. 6, 1995, available in WESTLAW, 1995 WL 2151645 (reporting that Citizens for a Sound Economy set aside a good part of its \$10 million budget to reform issues, Newt Gingrich's Progress and Freedom Foundation devoted \$500,000 to design a private drug approval process, and the Washington Legal Foundation started an advertising campaign against the FDA).

181 *Id.* See also, Annas, *supra* note 1.

182 See *supra*, note 10 and accompanying text.

company providing a drug and the physician prescribing it only increase and exploit the patient's suffering by providing drugs with a false promise of help and hope.¹⁸³ Problems of a perceived drug lag are, according to FDA supporters, the product of the inherent tensions in the incentives of a drug reviewer: if a reviewer approves an unsafe drug that later proves to have serious adverse events, the reviewer faces a maelstrom of public and Congressional anger for having approved the drug; however, if the reviewer fails to approve a beneficial drug, the failure will probably go unnoticed. ¹⁸⁴

While nothing as yet has concretely developed from all the rancor over the reform of the FDA, the debate and the criticisms leveled at the agency have spurred it to act on its own behalf. In an effort to provide quicker access to life-saving treatments for AIDS and cancer patients, the FDA has implemented a fast-track approval process, which allows marketing of these drugs after Phase II trials, and a treatment IND program, which allows certain patients expedited access to investigational drugs.¹⁸⁵ Legislation from Congress has given the FDA the authority to collect user fees from drug companies, which helps to fund additional reviewers and thereby reduce the

¹⁸³ Amas, *supra* note 1. Annas argues strenuously that the reforms implemented in the wake of the AIDS crisis have threatened to transform the [FDA] from a consumer protection agency into a medical technology promotion agency; and [have] put AIDS patients, already suffering from an incurable disease, at further risk of psychological, physical and financial exploitation by those who would sell them useless drugs. *Id.* at 772. He goes on to argue that true compassion for AIDS patients does not involve dispensing false hope or unreasonable hype, *Id.*, and that the strict scientific standards that have been used by the FDA prevent risk[ing] the health of all who later use a drug that has been too hastily approved. *Id.* at 797.

¹⁸⁴ Rutherford, *supra* note 1, at 214.

¹⁸⁵ See Hutt and Merrill, *supra* note 8, at 552-566 (discussing the effect of the AIDS crisis on the FDA's drug approval process). For explanations of fast-track approval and treatment INDs, see Walsh and Pyrich, *supra* note 1, at 950-51.

amount of time needed to review NDAs.¹⁸⁶ The FDA has also participated in conferences with its international counterparts with the intention of harmonizing international drug review standards.¹⁸⁷ Finally, the FDA has begun experimenting, on a limited basis, with contracting out some of its regulatory tasks to third parties.¹⁸⁸

With all the reforms it has implemented, the FDA has concluded that it is becoming more efficient and has offered the statistics to prove it. In his two most recent addresses to the Food and Drug Law Institute, FDA Commissioner Kessler has supported his conclusion that the FDA is a worldwide leader when it comes to the rapid and efficient review and approval of new drugs¹⁸⁹ with a stream of statistics showing a decline in the time the FDA requires to review and approve a new drug. The median time to approval has been steadily declining, reaching an all-time low of 15.1 months for calendar year 1996.¹⁹⁰ That decline has been true for all drugs, both

priority and standard, with priority drugs actually posting a median review time of 7.8

months.¹⁹¹ Comparing the FDA's performance with that of other countries, Dr. Kessler

¹⁸⁶ PRESCRIPTION DRUG USER FEE ACT, Pub. L. No. 102-571, 106 Stat. 4491 (1992).

¹⁸⁷ Katz, *supra* note 1, at 580.

¹⁸⁸ Walsh and Pyrich., *supra* note 1, at 973-8 1 (discussing the FDA's experience with private contracting and with working out the practical and legal problems associated with it).

¹⁸⁹ David A. Kessler, *Remarks By the Commissioner of Food and Drugs*, 51 FOOD & DRUG L.J. 207, 208 (1996) (reprinting speech made to The Food and Drug Law Institute's 38th Annual Educational Conference, Dec. 12-13, 1995) [hereinafter *Remarks 1995*].

¹⁹⁰ David A. Kessler, *Remarks By the Commissioner of Food and Drugs*, 52 FOOD & DRUG L.J. 1 (1997) (reprinting speech made to The Food and Drug Law Institute's 40th Annual Educational Conference, Dec. 10-11, 1996) [hereinafter *Remarks 1996*].

¹⁹¹ *Id.* at 2. The FDA labels certain drugs as priority drugs, when those drugs are

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concluded that the median times to approval for the United States are faster than those in the European Union (EU)¹⁹² and that the FDA is often the first country to approve most new drugs.¹⁹³ The posted efficiency improvements appear to have come without cost, as Dr. Kessler noted that no drug was withdrawn for either safety or efficacy reasons.¹⁹⁴

The improvements appear to be real. In its report before the House Subcommittee on Health and Environment, the General Accounting Office (GAO) concluded that [NDAs] are moving more quickly through the review and approval process and that the amount of time to obtain an approval is approximately the same in this country and in the United Kingdom.¹⁹⁵ The GAO reported a decrease in the time taken for NDA approvals from 33 months in 1987 to 19

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intended to treat serious illnesses or illnesses for which there are sub-optimal or no current treatments. Priority drugs receive expedited consideration in the drug approval process. Hutt and Merrill, *supra* note 8, at 529. NDAs entering the FDA are compared against a matrix [that classifies] NDAs according to chemical type and therapeutic potential to determine their priority for review. *Id*

192 *Id* at 4.

193 *Remarks 199S*, *supra* note 189, at 208.

194 *Remarks 1996*, *supra* note 190, at 5. The time frame defining the period in which no drug was withdrawn is unclear, but Dr. Kessler appears to be referring to calendar year 1996 up to the time of his speech.

195 Mary R Hamilton, *FDA Review Times*, General Accounting Office, Statement by the Director of Program Evaluation in Human Services Areas to the Subcommittee on Health and Environment, Committee on Commerce, House of Representatives, May 2, 1996, *available at* <http://www.access.gpo.gov> [hereinafter GAO Report]. Hamilton concluded that the consistency of all our results supports the conclusion that the reduction in time is real and not an artifact of how time is measured. *Id*

months in 1992.¹⁹⁶ The report also showed the FDA to be at least equivalent to the UK in the time it takes to review a new drug. In comparing the performance of the FDA and its UK counterpart with respect to eleven new drugs approved between 1986 and 1992, the GAO concluded that the approval times for NCEs in the US were actually shorter than those of the

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While the empirical data suggests real improvement at the FDA, critics remain dissatisfied with the FDA's performance. Critics say that the FDA's statistics focus only on the FDA's review time and not on total drug development time, which they claim is still abysmally long.¹⁹⁸ Because the FDA continues to adhere to strict testing requirements, an NCE spends too much time in the laboratory before finding its way to the market. Thus, reforms that would reduce the amount of data that an NDA must include and eliminate duplicative tests are still necessary.¹⁹⁹

B. Current Reform Proposals

Current reform proposals can be broadly categorized under three rubrics: (1) privatization proposals, (2) proposals aimed at adopting effective and efficient foreign drug approval procedures, and (3) miscellaneous proposals designed to address particular problems in the process. Analyzed against the backdrop of the Prozac controversy, however, each of these proposals fails in significant respects.

¹⁹⁶ *Id* at Chapter 0:3.

¹⁹⁷ *Id* at Chapter 0:4.3.

¹⁹⁸ See, e.g., *FDA Overhaul is Sought Despite Some Improvement*, CHEMICAL MIKT. REp. 16, Nov. 20, 1995, available in WESTLAW, 1995 WL 8079076.

¹⁹⁹ Walsh and Pyrich, *supra* note 1, at 93 6-7.

I. Privatization Proposals

(a) Summary of Current Privatization Proposals

Loosely speaking, privatization has become a short-hand expression for the idea of quicker, more efficient government.²⁰⁰ Its forms vary drastically, from complete dismantling of the FDA and the use of market incentives to police the safety and efficacy of drugs to allowing the FDA to contract with private groups on a limited basis to perform some of the tasks that overburden the agency. The guiding principle for all the forms of privatization positioned on the continuum is that the free market system guides the entity [the FDA] to make the most economically efficient (and therefore most desirable) decisions.²⁰¹ Many of the privatization reform proposals cluster around the central idea that at least some use of private groups and an explicit requirement for the FDA to consider both the costs and benefits of its actions during the course of the drug approval process would decrease the FDA's monopolistic control over the drug approval process and would promote more efficient results.

Leading the discussion on privatization, Congress has come forward with a range of reform proposals that all advocate some kind of privatization but that vary widely in how much authority the FDA would retain.²⁰² In the House of Representatives, Representative Ron Wyden

200 Rutherford, *supra* note 1, at 203.

201 *Id* Rutherford has summarized and synthesized many of the privatization proposals being debated at the time of her article. The proposals include creating time-based communication incentives, creating time-based economic action incentives, providing incentives to approve and removing disincentives to delay for FDA employees, requiring the FDA to make a cost-benefit analysis on all major future regulations, and relying on other bodies to provide safety and efficacy data. *Id* at 223.

202 The major bills mentioned here are more thoroughly discussed in Price, *supra* note
(continued...)

(D-Or.) introduced a bill providing for limited areas where domestic third parties could review drugs, biologics, and medical devices. A House Republican Task Force on FDA Reform introduced several bills that would greatly curtail the FDA's role by essentially limiting its function to that of exercising veto power over third party reviews. Striking a balance between these two proposals, Senator Nancy Kassebaum (R-Ka.) introduced a bill that allows for quicker approval of new drugs by statutorily decreasing the amount of time that the FDA has for review and, if the deadline is not met, allowing third-party review of the NDA. This bill would also allow one well-controlled study to prove the safety and effectiveness of the new drug²⁰³ and would create a category of automatic approval if the drug is approved by the UK or the EU. 2C14

Private organizations have made their own proposals, which have primarily been grounded in the principle that reliance on market incentives and the tort system will produce the proper incentive for manufacturers to produce safe and effective drugs.~ Most of these proposals envision the FDA's role as limited to that of an information provider. The Progress and Freedom Foundation, for example, would completely privatize the approval process, relegating the FDA to minimal oversight of third party reviewers and to conducting postmarketing surveillance of drugs

202(.. continued)

I, at 660-663.

203 *Streamlined FDA? Not So Fast*, NEWSL. - PEOPLE'S MED. SOC'Y 4, June 1, 1996, available in WESTLAW, 1996 WL 10159392.

204 Price, *supra* note 1, at 662.

205 Rutherford, *supra* note 1, at 205-6.

already on the market.²⁰⁶ While the details differ from group to group, most rely on third parties to oversee the preapproval process and industry to develop its own voluntary standards. The drug industry, speaking through the Pharmaceutical Research and Manufacturers of America (PhRMA) has advocated setting up a panel to review the FDA's performance.²⁰⁷

Some legal commentators have developed and advanced another proposal.²⁰⁸ Their scheme would create private certification bodies, which would work under the FDA's supervision and would assume responsibility for some of the FDA's regulatory tasks. Because the FDA is a politically accountable body with substantial expertise accumulated over the course of its existence, Walsh and Pyrich advocate delegating only those tasks that do not involve more weighty risk-benefit analyses. At all times, however, the FDA would retain ultimate authority over the decisions made by private entities.

Those advocating privatization have argued that numerous benefits to be gained by limiting the scope of the FDA's role in the approval of drugs make this mode of reform particularly desirable. Primarily, privatization would free resources for other aspects of the FDA's mission by delegating some of its current regulatory tasks.² Though there is little data to support the hypothesis, theoretically privatization would result in decreased drug development

²⁰⁶ Walsh and Pyrich, *supra* note 1, at 993-4.

²⁰⁷ Rutherford, *supra* note 1, at 207.

²⁰⁸ For a complete discussion of this proposal, see Walsh and Pyrich, *supra* note 1, at 998-1016.

²⁰⁹ Price, *supra* note 1, at 665. *See also* Rutherford, *supra* note 1, at 210; Walsh and Pyrich, *supra* note 1, at 955.

time and expense, making more safe and effective drugs available to consumers at lower cost.²¹⁰ Regardless, efficiency gains brought about by the use of third parties would decrease the costs associated with the current system. 211 Others have suggested that privatization may help to reduce the impact of politics on the approval process.²¹²

(b) *Critique of Privatization: Allowing only Limited Privatization*

Supporters of privatization are quick to dismiss the major objection to this mode of reform

– that private approval bodies, who will presumably have tighter links to the drug industry than the FDA currently does,²¹³ will shake the American public's confidence in the safety and efficacy of the drug supply because of a perceived lack of appropriate incentives to monitor safety and efficacy. The Prozac controversy, however, argues against dismissing that objection so easily. As the story of Prozac demonstrates, consumers will operate their own process of drug approval, regardless of the FDA's judgment of the safety and efficacy of a new drug, and in so doing will tolerate very little risk. In the absence of a politically accountable agency's review of new drugs, the costs of this informal process would escalate as consumers compensate for the lack an independent judgment of safety and efficacy.

The accountability that comes from having government make the decisions on the

210 *Id*

211 *Id*

212 Walsh and Pyrich, *supra* note 1, at 956.

213 Rutherford, *supra* note 1, at 207. This seems likely, as most proposals require the drug companies seeking review to pay the independent group to evaluate its drug.

marketing of drugs makes the current process acceptable to the American public.²¹⁴ Thus, any reform that diminishes that accountability will produce a crisis of confidence that will inhibit patients from accepting necessary drug treatments.²¹⁵ With militant opposition to Prozac and an intense fear over its safety, patients quit taking Prozac, whether or not advised to by their physicians.²¹⁶ This occurred even in the face of information provided by physicians, Lilly and the FDA that contradicted media accounts of a lack of safety, suggesting that consumers will not necessarily respond to information disclosure in deciding whether or not to accept a drug.

While stringent conflict of interest rules designed to combat appearances of impropriety may partially address the problem of acceptability of a privatized process, the problem is not solved. The American experience with the approval of new drugs has developed from a politically accountable governmental body; thus, overcoming the perception of diminished accountability will be difficult. In fact, having an accountable agency does not guarantee the public's confidence in a new drug.

The accountability argument can only go so far, though, for some of the privatization proposals limit third party assumption of FDA tasks to narrow areas where the FDA expends resources on tasks that divert its attention from more important concerns. A limited role for

²¹⁴ Harvey Teft *Drug Approval in England and the United States*, 33 AM. J. COMP. LAW 567, 580-81 (1985).

²¹⁵ See Walsh and Pyrich, *supra* note 1, at 966-71 (discussing the problem of accountability by private organizations).

²¹⁶ *Supra*, notes 87-89 and accompanying text.

privatization, along the lines of that proposed by Walsh and Pyrich,²¹⁷ might be appropriate. Limited privatization gives third parties responsibility for FDA tasks such as the review of generic drug applications and the inspection of manufacturing and research facilities for compliance with FDA regulations.²¹⁸ By delegating only those tasks that do not involve more sensitive concerns and the more important decisions about safety and efficacy, limited privatization would not compromise the acceptability of the approval process. At the same time, however, adopting limited privatization could achieve some of the benefits that supporters of privatization cite, such as the release of resources for other purposes.

2. Adoption of Foreign Procedures

(a) Summary of Current Proposals

Some commentators have approached the problem of determining how to reform the FDA by comparing the US system with the systems of foreign countries. These analyses have generally concluded that the US could decrease the drug lag by either adopting some of the procedures of foreign countries or by relying on the data developed during another country's process.

One form of comparison has focused on the drug approval system set up in the UK and on the difference in timing between the two systems.²¹⁹ While the UK focuses its efforts on postmarketing review of the claims made before marketing, the FDA operates a front-end-loaded

²¹⁷ *Supra*, note 208 and accompanying text. This proposal will be referred to as limited privatization.

²¹⁸ *Id* at 1002-1009.

²¹⁹ The rationale for this comparison is that the US and UK have substantially similar systems, but the UK manages to approve drugs for marketing much more quickly. See Diliman, *supra* note 1, at 931.

system of approval, requiring extensive demonstrations of safety and efficacy before the drug goes on the market.²²⁰ Contributing to and accounting for this difference is the underlying British philosophy of drug approval, which is said to accommodate more readily the

unpalatable truth that the research process continues even after a licensed drug has been made available for general prescription, and that serious, rare side effects will not necessarily manifest themselves until a drug has been used by a far greater proportion of the population than is feasible even with extensive pre-market testing.²²¹

Specifically, the UK cuts the amount of test data necessary prior to approval; for example, preclinical testing consists of only six month chronic toxicity studies in two animal species prior to clinical testing.²²² As long as no serious problems occur with the drug in clinical testing, the drug is placed on the market, and most of the proof of safety and efficacy arrives postmarketing. The UK has an established system for physicians to report adverse drug reactions directly to the regulatory agency, a system that has been more widely used than its US counterpart.²²³ In order to identify and minimize potential harm from a new drug, the UK may limit the ability to prescribe it to hospital pharmacies or certain medical specialists.²²⁴

Advocates of adopting a British approach to drug regulation argue for altering US

²²⁰ See Relihan, *supra* note I, at 246. For a thorough comparison of the two systems, see Dillman, *supra* note 1, at 925-35.

²²¹ Teft *supra* note 214, at 579. The FDA and medical experts accept this idea that drugs are not fully tested prior to marketing. See *infra*, note 226 and accompanying text. However, it has not been accommodated into the existing drug approval scheme.

²²² Dillman, *supra* note 1, at 931. Cf. to the one year of animal testing required by the FDA. *Supra* note 16.

²²³ Relihan, *supra* note 1, at 245.

²²⁴ Teft *supra* note 214, at 579.

procedures to fall more in line with the UK, primarily by shifting the FDA's emphasis to postmarketing surveillance. One version of this proposal advocates reducing Phase III clinical trials and increasing postmarketing surveillance.²²⁵ In structuring this proposal, Wardell argues that Phase III testing is largely duplicative, because by the end of Phase II testing most drug testing has developed general evidence of overall efficacy, the most common adverse reactions, and the most obvious precautions for use. The NDA could be submitted at the beginning of Phase II testing and reviewed concurrently with Phase II trials; alternatively, a preliminary NDA could be submitted and the remainder of Phase II data submitted at the end of the review process.

By shifting the focus of regulation to postmarketing surveillance, advocates argue that the reduction in the premarketing approval process would allow drugs to be marketed sooner and at less cost, while at the same time regulators could maintain a safe and efficacious drug supply through vigorous postmarketing surveillance designed to provide the means for swift reaction to problems that develop in the use of the drug. Advocates of this approach point out that this is the de facto result of the current FDA system. In spite of its focus on premarketing testing, the FDA cannot make complete determinations about the safety and efficacy of a drug, because no matter how large or thorough a clinical trial is, it cannot uncover every problem that can come to light once a product is widely used.²²⁶ Thus, the FDA obtains little more evidence of safety and

²²⁵ William Wardell, *Can Improved Postmarketing Surveillance Permit Earlier Drug Approval?*, 12 DRUG THERAPY 143 (Feb. 1982). Wardell does not believe that all drugs are appropriate for this kind of review, but those drugs that are could be identified early in Phase II.

²²⁶ Kessler, *supra* note 46, at 2765. Because a drug can be tested in only so many human subjects before it is approved, the studies accompanying an NDA will not reveal reactions with an incidence rate of one in five thousand, one in ten thousand, or in some cases, one in one thousand. *Id.* The limits of premarketing testing have been noted by others besides the FDA.

(continued...)

efficacy before marketing than its UK counterpart, while relying on its system of postmarketing surveillance, primarily the MIED WATCH program, to catch any problems that later develop.²²⁷ Because of its unique advantages, this particular proposal, shifting the timing of FDA regulation, will form the basis of the proposal outlined in Part V.

Another proposal has been to advocate some form of harmonization of the FDA's standards with those of other sophisticated drug -producing and -consuming countries, such as the UK, the EU, and Japan. This mode of reform would develop international standards for preclinical and clinical testing, which would then allow the FDA to accept data from tests conducted in other countries. One specific proposal has advocated producing an international treaty on premarketing drug approval requirements.²²⁸ The FDA has already begun moving toward this goal by participating in the International Conferences on Harmonization, designed to develop uniform guidelines that will assist the participating countries in developing harmonious regulations related to the development and testing of new drugs.²²⁹

A variation of this proposal argues for according some kind of evidentiary status to other

226(.. continued)

~The detection of ADRs [Adverse Drug Reactions] is inhibited by the five too's of premarketing trials: too few [test subjects], too simple [because patients tested do not have any medical problems other than those the drug is supposed to treat], too narrow [because patients receiving concurrent drug therapy are excluded from the samples], too median-aged [because the young and the elderly are generally not tested], and too brief Scott et al., *supra* note 53, at 1785.

227 The reality of drug testing, however, indicates that problems will develop, for precisely the reasons outlined *supra*, note 226 and accompanying text.

228 Wall, *supra* note 175, at 339.

229 Joseph G. Contrera, *The Food and Drug Administration and the International Conference on Harmonization: How Harmonious will International Pharmaceutical Regulations Become?*, 8 ADMIN. L.J. AM. U. 927 (1995).

countries' findings.²³⁰ For example, in the legislation introduced by Senator Kassebaum, new drugs approved in the EU or the UK could receive deemed approval status in the US. If the FDA does not complete its review of an NDA and take some affirmative action with respect to the drug within thirty days of the statutory deadline, a sponsor who has received approval from either the EU or the UK could have its drug deemed approved on the basis of the foreign approval and then proceed to market it.²³¹

In another proposal, approval by the EU's new regulatory authority, the European Medicines Evaluation Agency (EMA), would trigger two statutory occurrences: (1) the EMA's approval would constitute substantial evidence of efficacy, thereby reducing the need for much of the clinical testing that would otherwise be conducted in the US, and (2) EMA approval would trigger a 180 day period in which the FDA would review the same drug, with the FDA's failure to act within that time period resulting in automatic approval for the drug to be marketed in the US.²³² Because the EMA would adhere to similarly rigorous standards for research and scientific evidence, the FDA would arguably gain nothing by putting a new drug through its own paces.²³³

Carrying this argument further, some advocates say that practical reality may force the

²³⁰ This has been one of the proposals advocated by PhRMA. Rutherford, *supra* note 1, at 207.

²³¹ Price, *supra* note 1, at 662.

²³² Note, *supra* note 1, at 20 18-20.

²³³ Indeed, it may turn out to be true that the EMA standards of proof for new drugs are more rigorous than those imposed by the FDA. Note, *supra* note 1, at 2019 (citing Katz, *supra* note 1, at 585).

FDA to adopt the findings of the EMIEA. The size of the EU market and its profit potential would make it more attractive for drug companies to seek approval from the EU first; thus, many of the initial resources that go into drug development would conform to the EMEA's testing requirements rather than the FDA's testing requirements. If drug companies were to gear their drug development toward EMEA approval, the US would be faced with a longer drug lag. Thus, in order to get new drugs into American consumers' hands, the FDA would have to accept the EMIEA's findings.²³⁴

(b) *Critique of the Adoption of Foreign Findings*

The FDA has been participating in the International Conferences on Harmonization, which have sought to standardize the testing requirements for drug companies in all countries so that participating countries can rely on data collected in each country. It would be premature, however, to place a statutory overlay onto this process, which would *require* the FDA to review a drug approved under another country's scheme expeditiously or to accord another country's approval decision deemed approval status. As the International Conferences on Harmonization make clear, there are numerous differences in the processes of the various sophisticated drug-producing countries. Until those differences in standards can be smoothed out, statutory implementation of a requirement that international data have a certain evidentiary value is unwise.

The EMEA provides the best reason for allowing the FDA to harmonize its procedures with international counterparts by itself. Because the EMEA is a new agency and experience with its results is very limited, exactly what deemed approval status for drugs approved in the EU would mean is difficult to tell. In addition, the proposals that would shorten drug development

²³⁴ Note, *supra* note 1, at 2021.

time by giving the EMEA's approval a certain evidentiary value do not adequately account for the EMEA's process. The statute creating the EMEA actually authorizes two procedures for approving a new drug.²³⁵ The first procedure, the centralized procedure, is a process that, at least currently, will only be used for some pharmaceutical products. Under the centralized procedure, the new drug product is evaluated according to the procedures used by the EMEA, which will require adequate evidence of safety, efficacy and quality. The second procedure, the decentralized procedure, makes use of the drug approval processes currently in use in each of the EU's Member States. Once a Member State approves a drug for marketing, the drug's sponsor can apply for mutual recognition by all the Member States. The other states must recognize the approval and allow the drug onto the market unless there are grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health.²³⁶ This decentralized procedure of mutual recognition will become mandatory after January 1, 1998.²³⁷ Thus, a statutory requirement could force the FDA to accept a drug onto the US market that has undergone its only scientific testing according to the requirements of countries with less stringent in their standards than the US, the UK and other sophisticated countries simply because, as a legal matter, the EU or the UK has approved the marketing of the drug based on the mandatory mutual

²³⁵ Richard F. Kingham et al., *The New European Medicines Agency*, 49 Food &

DRUG L.J. 301(1994). Kingham *et al.* Provide a thorough explanation of the new EMEA drug approval process. An explanation of the centralized procedure for drug approvals begins at 306.

An explanation of the decentralized procedure begins at 309.

²³⁶ *Id* at 311 (internal quotation marks omitted).

²³⁷ *Id*

recognition scheme. The result is likely to erode consumer confidence in the drug supply. 238 Countering this objection, supporters of adopting a deemed approval requirement for the

FDA argue that the erosion of consumer confidence in the US that would occur by automatically approving drugs subject to less stringent testing standards can be combated by having the FDA take seriously its authority to veto drugs coming into the US through the deemed approval process.²³⁹ However, because the deemed approval process creates a statutory presumption that approval in another country means that the drug is safe and effective, the FDA would have to develop adequate evidence to combat that presumption, something that could require more review than the thirty days most proposals give the FDA to object to marketing of drugs approved in other countries. Moreover, if at any time the FDA lacked the resources to compile the evidence to rebut the presumption, its veto power would become ineffective. Finally, any risk-benefit calculus used by another country in order to determine whether or not to approve a drug will reflect the unique assessments by that country's political process of what risks and benefits should count and how they should be weighed. That calculus will not necessarily reflect the risks and benefits that risk-averse Americans would consider acceptable.

In addition to the foregoing objections, one must ask what is to be gained by legislative imperatives on the acceptance of foreign data and foreign findings. For this kind of reform to succeed, the FDA would have to adopt guidelines for the acceptance of foreign data that would guarantee that the drugs that are proposed for marketing in the United States have been subjected to the same rigorous requirements that the FDA itself would require. For example, for the use of

²³⁸ Price, *supra* note 1, at 670.

²³⁹ *Id*

EMIEA approval as substantial evidence of efficacy to require the same quality of proof achieved under the current system, the FDA would also have to determine the weight to be accorded the evidence produced by the two different procedures for approval in the EU. The FDA has already begun this process and has the substantial expertise and experience to determine what foreign approval procedures and data are appropriate for it to consider. A statutory requirement is not only premature but would also prevent the country-specific determinations about foreign procedures and data that must occur in order to allow in only those foreign-approved drugs that are safe and effective.

For example, while it is logical to conclude that using EMEA approval to demonstrate substantial evidence of efficacy would shorten overall drug development time, one must ask whether EMEA approval should always be afforded this evidentiary value. Moreover, which EMIEA approval process – centralized or decentralized – would be sufficient to constitute substantial evidence of efficacy? Relying on the FDA to answer those questions would ensure

that drugs that take advantage of this proposal would still live up to the stringent standards of the

FDA.²⁴⁰

3. Miscellaneous Reform Proposals

(a) *Summary of Miscellaneous Proposals*

²⁴⁰ A statutory requirement for the adoption of foreign findings reflects nothing more, it seems, than an inherent distrust of the FDA to take advantage of useful information developed in other countries, which is born of the legislative knowledge that the FDA has not always acted responsibly in weighing what foreign data is acceptable. While the FDA once refused to consider data even though its current experience with accepting foreign data demonstrates that there should never have been a problem, even now, in accepting foreign data, the FDA has not done so unthinkingly. Instead, it has been involved in international efforts to ensure that the data it does accept will be acceptable according to its own standards. *See Contrera, supra* note 229.

Other proposals for reform have advocated specific measures designed to address particular problems that arise out of the operation of the current system. Primarily, critics of the current system have argued for the need for tort reform. With such a stringent approval system in place and because of the expense associated with meeting regulatory requirements, these advocates argue that allowing recovery for drug-related injuries merely drives up the cost of new drugs.²⁴¹ Some have argued that regulatory compliance should be a complete defense in tort,²⁴² while others have suggested a statutory compensation scheme, similar to Workers' Compensation, that provides compensation to those injured without forcing a larger tax on new drugs in order to account for spiraling tort liability.²⁴³ In any case, tort reform is a necessary component of any regulatory reform.² Reform proposals should at least account for the extent to which drug-related injuries are compensated, for that helps to determine how much premarketing regulation is necessary.²⁴⁵

Noting that the drug lag surfaced after the 1962 Kefauver-Harris Amendments required

241 Walsh and Pyrich, *supra* note 1, at 1016; Teft *supra* note 214, at 606-608.

242 For example, the Progress and Freedom Foundation has advocated this position. Walsh and Pyrich, *supra* note 1, at 993-4.

243 Teft *supra* note 214, at 608. This suggestion is not explained in any great detail.

244 Any reform of the FDA will also have to result in tort reform for drug-induced injury in order to address the changes brought about by the reform. However, this issue is beyond the scope of this paper as it requires, for proper treatment, an extensive analysis of the current system and the available alternatives. For purposes of the proposal outlined *infra*, it is assumed that the current tort system remains in place, with plaintiff able to sue for any alleged harm caused by a drug but with difficulties of scientific proof making recovery unlikely. See TeW *supra* note 214, at 606-7 (explaining why the notion that market deterrence can operate satisfactorily through the compensation mechanism is particularly difficult to sustain in respect of drugs).

245 Teft *supra* note 214, at 606.

proof of efficacy prior to marketing, others have advocated removing or curtailing the efficacy requirement, leaving the FDA responsible only for the safety of new drugs. Beckner has developed the most convincing argument for this approach, arguing that the most effective correction of market failures... is usually the one that directly addresses the market failure.² Beckner advocates altering the current process to compensate for the market's disincentive to provide adequate information on efficacy by mandating strict information disclosure rather than by requiring premarketing proof of efficacy.²⁴⁷ Others, including Senator Kassebaum²⁴⁸ and PhRMA²⁴⁹, would reduce the requirement from two well-controlled studies of efficacy to one.

(b) *Critiquing the Removal of the Efficacy Requirement*

While it appears attractive to remove the efficacy requirement and limit the FDA to responsibility for the safety of drugs because of the expected decrease in drug development and approval time, this proposal would eliminate the benefits gained by requiring some proof of efficacy. This elimination, for reasons discussed below, would be unambiguously unethical. The specific example of the effect of removing the efficacy requirement for antidepressants shows that this reform could also cost as much as it might gain.

Patients receiving treatment are expected to give informed consent to the treatment,

²⁴⁶ Beckner, *supra* note 1, at 560.

²⁴⁷ *Id.* at 560-i.

²⁴⁴ *US Far-Right Groups Target the FDA*, *supra* note 180.

²⁴⁹ Rutherford, *supra* note 1, at 207.

except in limited circumstances.²⁵⁰ If a physician offers a drug to a patient but cannot state affirmatively that the drug has been proven to be effective for the condition being treated, then, as a practical matter, the patient ought not to give consent. If the patient does consent to the treatment, then the patient is not consenting to anything meaningful, because the patient is not consenting to a treatment. Though it can be argued that the patient could provide meaningful, informed consent to the fact that the drug may not be effective, in this case the patient is essentially consenting to serve as a test subject for the drug. As a research subject, the patient then should, at the very least, not be required to pay for the treatment, as the benefit gained from having the patient use the drug belongs to the manufacturer. Others have carried the ethical argument farther, arguing that research subject/patients' capacity to provide informed consent is diminished because of the coercive power of the offer of treatment in this situation,²⁵¹ making greater safeguards for the protection of the patient necessary.

Providing drugs that have not been proven efficacious also takes advantage of patients, causing them to suffer needlessly and driving up the costs of their care.²⁵² For example, antidepressants require several months of treatment before the patient and the physician notice the

250 Patients in emergency need of treatment and patients who lack the ability to provide meaningful consent to treatment, such as minors and incompetents, are generally excluded from informed consent rules.

251 Annas, *supra* note I, at 777 (citing F.J. Ingelfinger, *Informed (But Uneducated)*

Consent, 287 NEW ENG. J. MED. 465, 466 (1972) (noting that all research volunteers are subtly coerced to provide consent but that these pres~es... are but fractional shadows of those enclosing the patient-subject. Incapacitated..., and fearful for his health and perhaps life, he is far from exercising a free power of choice when the person to whom he anchors all his hopes asks him to consent to experimental treatment) (internal quotation marks omitted)).

252 *Supra* note 183 and accompanying text.

full beneficial effect. Moreover, antidepressant therapy requires a trial-and-error process, which can be lengthy, to determine the proper treatment.²⁵³ If the patient receives a drug that is not effective, the individual and social costs imposed by the months of waiting to determine whether or not there will be a therapeutic effect are substantial²⁵⁴ and the patient will suffer needlessly. Thus, doing away with the efficacy requirement does not provide a suitable answer to the question of how to reform the drug approval process.

V. Reforming the FDA's Drug Approval Process: Learning from Prozac

Because the current proposals have the limitations outlined above, there needs to be another way to go about deciding how to reform the current FDA drug approval process; thus, this section will first present a new approach for determining how to reform the process. Then, using the analysis of the premarketing testing of fluoxetine, this section will propose reforms that are tailored to remedy the problems seen in that process. Applying the functional approach to antidepressants, the analysis of Prozac developed in this paper shows how drug development time could be shortened without compromising safety and efficacy.

A. Separate Treatment for Individual Classes of Drugs: A Functional Approach

²⁵³ Psychiatrists are advised to begin antidepressant therapy with a 6-12 week trial

during which the physician selects a drug, experiments to find the correct dose and to ensure that there is some therapeutic effect for a few weeks, and monitors side effects. At any time during this trial, the psychiatrist may change the drug because of uncomfortable side effects or lack of therapeutic effect, which begins the 6-12 week trial anew. At the end of twelve weeks, the psychiatrist might change the medication because of a plateau in the patient's improvement, which results from the drug's not being fully effective. Otherwise, the patient should continue on drug therapy for four to nine months. Delgado and Gelenberg, *supra* note 132, at 270-74. If a patient and physician use antidepressants not known to be effective during this process, it could be a substantial period of time before the patient is taking a therapeutic drug.

²⁵⁴ *Supra* note 123.

Reform should proceed by means of a functional approach, which separates drugs into categories, considers the reform measures that are necessary and proper for each category, and implements reform measures according to what is appropriate for each category. As the issue is currently approached, reformers consider proposals based on the perceived drug lag or based on the argument that patients with life-threatening diseases are being deprived of needed drug treatments. As a result, they tailor the proposals and the measures implemented around the need to address the problems associated with getting life-saving treatments onto the market faster. However, these measures fail to address what would happen in the case of drugs taken for chronic conditions or drugs designed to treat illnesses where the risk-benefit calculus is dramatically different from that considered in connection with an illness, such as AIDS or cancer, that will in most cases be terminal.

Economically, this functional approach makes sense. When faced with a drug where the potential benefits are substantial compared with the risks, the cost of delaying the drug's entry onto the market is potentially large.² For example, consider AIDS drugs. There are currently no known cures for AIDS. If a drug has the potential to cure the disease, its benefits would be substantial, not only in the lives saved immediately but also in the ability to treat those who are currently HIV-positive. By delaying the time it takes to get the drug to the market, many AIDS patients would have died or would have progressed to the point that any treatment would no longer be effective.

While patients with terminal diseases have been correctly characterized as having little to

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The basis of this argument is found in Mendeloff *supra* note 1, at 209.

lose and much to gain,²⁵⁶ that perspective is not necessarily shared by patients with other illnesses, such as depression. Prior to the marketing of Prozac, there were treatments available for depression that could be used, though patients did not always comply with them.²⁵⁷ In discovering this new treatment, its benefits were not so easily quantifiable. While Prozac was clearly a safer drug to place in a potentially suicidal patient's hands, no one knew for certain how effective the drug would be in treating depression. Thus, it would not necessarily prevent more deaths than it might cause. Accordingly, the cost of delaying its entry onto the market in order to undergo premarketing approval would be less than that of an AIDS drug, because patients would be able to receive other treatments in the interim period between discovery and marketing. By requiring the same level of proof of safety and efficacy for both AIDS drugs and antidepressants, the FDA has imposed a greater cost on American citizens suffering from AIDS than on those suffering from depression. Thus, a lower standard of proof for the AIDS drug would bring the drug to the market earlier, thereby reducing the costs associated with the approval of the AIDS drug.²⁵⁸ A lower standard of proof for Prozac, though, could have put the drug on the market even though it might not have been effective. Thus, the cost imposed on society is to place patients on a drug that does not work, while the patient bears the cost of an extended period of time of suffering from depression.²⁵⁹ Therefore, different standards would reflect the unique positions of patients with different illnesses, and an approval process tailored to the unique

²⁵⁶ Dillman, *supra* note 1, at 944.

²⁵⁷ See *supra*, note 67-68 and accompanying text.

²⁵⁸ Mendeloft *supra* note 1 at 209-10.

²⁵⁹ See *supra*, note 123 (discussing the costs associated with depression).

position of patients with particular illnesses would allow the FDA to account for those differences and for the difference in the risk-benefit calculus. 260

Moreover, requiring the same process for all drugs may be inefficient because there are unique variables that a process designed to serve all categories of drugs does not account for; thus, by breaking the drugs down by category, a functional approach would determine the kinds of testing appropriate for each category. This would omit the costs associated with testing that provides only a tangentially related piece of information about the drug.

For example, with antidepressants, the extensive animal testing required is not necessary or helpful because of the lack of good animal models of depression; thus, the conclusions that can be drawn, based on animal testing, about the effect of an NCE on a psychiatric condition are limited. It is well known within the scientific community that there are no good, comprehensive animal models of depression.²⁶¹ In simulating depressive symptoms in animals, researchers often use a form of conditioning, whereby the animal is continually thwarted in its effort to reach a desirable goal. Animals conditioned in such a manner frequently exhibit symptoms associated

260 At least implicitly, the FDA already does this. Certain drugs are determined to be

priority drugs and, as such, receive an expedited review once the NDA has been filed. *Supra*, page ??.

261 William T. McKinney, *Basis of Development of Animal Models in Psychiatry: An Overview*, in ANIMAL MODELS OF DEPRESSION, *supra* note 169, at 3(... there is no such thing as a comprehensive animal model for depression, mania, or, for that matter, of any psychiatric syndrome. Furthermore, there never will be). *See also*, P. S.J. Spencer, *Animal Models for Screening New Agents*, 3 SuPP. BRrr. J. CLIN. PHARMACOLOGY 5 (1976) (So little is known about the aetiology and pathophysiology of the mental conditions we are attempting to combat, that the neuropharmacologist is unable to create typical, specific, model conditions in animals suitable for the detection and evaluation of new agents); Jacqueline N. Crawley, et al, *Animal Models of Self-Destructive Behavior and Suicide*, 8 THE PSYCHIATRIC CLINICS OF NORTH AMERICA 299, 299 (1985) (noting that animal models cannot be made to illustrate the complexities of human psychopathologies).

with depression in humans. On this basis, an NCE is introduced to attempt to relieve those symptoms. Those symptoms, however, are poor reflections of naturally-occurring depression (or other psychiatric illnesses), and may often be a better model of a general 'stress adaptation response' than of any specific clinical disorder.²⁶² When not using these methods of inducing depressive symptoms in animals, investigators will induce the symptoms in the animal by means of another chemical, such as reserpine.²⁶³ Thus, animal testing could not possibly reveal much at all about the potential therapeutic value of a drug for naturally-occurring psychiatric conditions, and this was true with the animal testing of fluoxetine.²

Against this category-by-category consideration of reform stands the objection that splintering the consideration of reform would itself be inefficient. Looking at the drugs by category would require an enormous proliferation of regulations and guidelines for all the different categories of drugs available and the time and resources spent in making category-specific rules could be better spent in other ways. In addition, the process of making a category-specific review of drug approval requirements would be costly.

In fact, though, the cost may not be prohibitive if the FDA could make use of its expertise to accomplish this approach. The FDA may already adhere to a kind of category-specific review through its use of expert advisory committees, which would provide a mechanism for reducing the costs associated with category-specific definition of the process. These committees are composed

²⁶² Dan J. Stein, et al. *Behavioral Disorders in Veterinary Practice: Relevance to Psychiatry*, 35 COMPREHENSIVE PSYCHIATRY 275, 281 (1994).

²⁶³ See *supra* notes 169-170 and accompanying text (discussing the limitations of reserpine-induced models of depression).

²⁶⁴ *Id*

of specialists in various areas who advise the FDA regarding drugs in specific categories.²⁶⁵ These expert panels would be in a unique position to influence and make determinations about the appropriateness of the approval process and its testing requirements for drugs within their specialty. The institutional costs, therefore, of tailoring the approval process along category-specific lines would not necessarily be great. While it would require a considerable effort to examine the categories of drugs separately, a drug approval process tailored to the specific needs and requirements of various drugs would have the advantage of streamlining approval of all the drugs within that category without compromising safety and efficacy.

Another objection to this approach is that individual patients suffering from each of the diseases all have the same calculus – the benefits to them of receiving a drug will outweigh the costs of a lower standard of proof; thus, the analysis supporting category-specific consideration is fundamentally flawed. However, such a subjective measure of the risk-benefit calculus for individual patients should not influence the overall process of applying a functional approach to reform analysis. Viewing the larger picture, it is quite clear that the benefits and risks are different for a patient suffering from a terminal disease than for a patient suffering from a chronic condition.

More to the point, however, is the objection that the lessons learned about one category of drugs are equally applicable to all drugs; thus, the determinations made when considering Prozac in isolation are not unique to psychiatric drugs. For example, the current drug approval process

265 The Psychopharmacological Drugs Advisory Committee, for example, is the advisory committee responsible for making recommendations to the FDA on drugs that act on psychiatric conditions – the psychotropic medications – for treatment of diseases such as depression and schizophrenia.

as a whole has been criticized for relying too heavily on animal studies.²⁶⁶ That proposition cannot be verified, however, absent a category-specific consideration of the need for reform. While it may be true that category-specific consideration will ultimately yield the same approval process for all drugs, the time spent considering the drugs by category will result in a drug approval process that can affirmatively be said to be the most efficient process for each drug category.

At least one commentator has suggested that the FDA's current bias toward stringent standards of proof and exacting requirements for proving safety and efficacy are correct and that these standards should be uniform for all drugs.²⁶⁷ Responding to the efforts to expedite approval of AIDS drug treatments, Annas argues that where the illness is life-threatening, doing anything other than requiring the drug to undergo the same rigorous procedures to prove safety and efficacy produces false hope for patients and lengthens the time it takes to develop a truly effective remedy for the illness. Annas, however, ignores the reality that the current system of drug approval in use at the FDA has imposed severe costs on the American public by delaying

²⁶⁶ Dillman, *supra* note 1, at 93 8-9 (noting that animal models provide weak results in determining drugs' effects on higher human functions, such as the central nervous system, that animal testing does not reveal all the toxic effects associated with a drug or predict drug interactions, and that when the risks and benefits of a drug are weighed according to the results of animal testing, drugs of clear value are withheld).

²⁶⁷ Annas, *supra* note 1. Annas suggests that uniform procedures may in fact be legally required, under U.S. v. Rutherford 442 U.S. 544 (1979). The Supreme Court held that the FDA was within its authority to refuse to prove laetrile as a cancer treatment, because the FDCA did not authorize the statutory requirements of safety and effectiveness to be deemed irrelevant for patients with certain diseases. The plaintiffs had argued that even though laetrile was unproven as a safe and effective treatment, they should be able to receive it in the US because their illness was terminal. Defining the procedures for testing, however, falls within the agency's discretionary power, as nothing in the functional approach would remove the statutory requirement that drugs be proved safe and effective.

safe and efficacious treatments and driving up the price of pharmaceuticals.²⁶⁸ The functional approach would merely develop the most efficient means for achieving the end of putting only safe and effective drugs on the market.

2. Shortening Drug Development Time

The analysis of the premarketing testing of fluoxetine showed two clear problems with the standard testing requirements: (1) the process increased the cost of developing fluoxetine and delayed its entry onto the market by requiring unnecessary tests; and (2) the clinical testing did not establish either safety or efficacy under the conditions that most patients would use the drug.

First, because animal studies do not clearly elucidate the therapeutic effects that a drug

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might have,² requiring preclinical data to establish potential therapeutic value is inefficient and unnecessary. Thus, the company should not have had to demonstrate the therapeutic potential of

fluoxetine through animal testing.²⁷⁰ Had this requirement been foregone for fluoxetine, the process would have cut down on the four years of animal testing that fluoxetine underwent,²⁷ allowing clinical testing sooner.

One might argue that the studies of fluoxetine's effect on reserpine-induced depression at

²⁶⁸ Price, *supra* note 1, at 657-658 (the drug lag has cost. . . U.S. consumers untold losses by decreasing their ability to select among beneficial therapeutic alternatives).

²⁶⁹ *Supra* notes 261-263 and accompanying text.

²⁷⁰ This argument should not be interpreted to mean that all animal testing should be forgone. Clearly, proof of safety in animals is a necessary prerequisite to human testing. There are other reasons for using animal tests in the drug development process. *Supra* note 261. All this argument stands for is the proposition that where animal testing data is unhelpful or only tangentially informative, the approval process should not require that information.

²⁷¹ See *supra*, notes 60-61 and accompanying text.

least signaled the possibility of a therapeutic effect from the use of fluoxetine in humans, and, without at least some indication of therapeutic effect, it would be unethical to allow patients to undergo clinical trials. Drawing an inference between studies linking serotonin levels to depression and the fact that animal studies confirmed that fluoxetine acted selectively on serotonin, however, could have established the potential for therapeutic value. Thus, if the requirement of animal proof of therapeutic potential is retained, then the level of proof necessary to establish the potential should be expanded to allow the drawing of such an inference. Otherwise, animal testing adds little to the information collected about fluoxetine and wastes resources which could have been used on expanded clinical trials of fluoxetine's efficacy.

Second, although most patients would be taking fluoxetine for several months, clinical testing occurred in only four to six week trials; thus, the approval process did not elicit information on safety and efficacy that was relevant for most patients. While this would seem to argue for more clinical testing, there are limits to what premarketing testing can achieve. ²⁷² A more palatable remedy for the lack of long-term data is a variation of the plan proposed by Wardell.²⁷³ Thus, by amending testing requirements to lengthen the clinical trials in Phase H, testing would approximate more closely the conditions under which most patients would take the drug for ²⁷⁴ On Wardell's theory that Phase III testing will not reveal much more than the general information already gathered on safety and efficacy, Phase III testing could then be

²⁷² *Supra* note 226 and accompanying text.

²⁷³ *Supra* note 225 and accompanying text.

²⁷⁴ For example, the clinical trials could run for eight to ten weeks, which would more closely approximate the period of time most patients would be using the drug.

eliminated and the NDA reviewed after the completion of Phase H testing.

This approach of increasing the length of the clinical trial may have addressed one of the shortcomings of the fluoxetine studies. The review of the SBA noted that the proof of efficacy was limited.²⁷⁵ Given that antidepressant efficacy is not generally established until the patient has been on antidepressant therapy for several months, though, longer clinical trials may have provided the additional data necessary to establish more convincingly that fluoxetine was effective in treating depression.

In making his proposal, Wardell explicitly excluded psychotropic medications from those that would be suitable for his proposal, because these medications are usually used by chronically ill patients for long periods of time, making it unsuitable to bring them to market without further testing of safety and efficacy. However, this objection ignores the fact that the clinical testing done in Phase III uses only four to six week trials, providing no additional information about long-term use than that already obtained in Phase H testing. Thus, a better procedure would require tests of a longer duration during Phase II, approximating more closely the normal conditions of use, and then proceeding to review the data for approval to market.

A more compelling objection is that lengthening the time taken for clinical trials exposes those control patients taking placebos to an unacceptable length of time without any treatment. Any use of placebos with control patients is ethically problematic, though,²⁷⁶ and the objections raised here are no less valid than they are when raised about all drug testing. To remedy the problem in this context, one of two adequate and well-controlled investigations could test the

²⁷⁵ *Supra* notes 158-174 and accompanying text.

²⁷⁶ *Supra*, note 166.

drug with a placebo in a shorter trial, while the other adequate and well-controlled investigation could test the drug against a standard treatment in a longer trial.

3. Improving Postmarketing Surveillance

By decreasing the amount of premarketing data required, the FDA would have to shift its resources toward greater postmarketing surveillance in order to maintain a safe and efficacious drug supply. The FDA has made great strides in this regard by implementing the MEDWATCH system, however, US rates of reporting by physicians remain low.²⁷⁷ Though the FDA has undertaken to combat the problems that are perceived to be the reasons for non-reporting,²⁷⁸ any shift away from premarketing processes and toward a reliance on postmarketing surveillance will have to address the problem of low reporting rates. ²⁷⁹

²⁷⁷ American Medical Association, *supra* note 51, at 361. Several reasons are given for this: a lack of awareness of how MED WATCH works, complacency about drug safety, fear of legal liability, guilt about having harmed a patient, and uncertainty about causation. *Id*

²⁷⁸ For example, the rule pre-empting state and local law on disclosure of MED WATCH reports is an effort to address physicians' fears of legal liability if their reports to the FDA are discovered.

²⁷⁹ A study reported in the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION and

conducted under the auspices of the FDA attempted to determine what would stimulate physicians to become more active in submitting adverse drug reaction (ADR) reports. The study involved the Rhode Island Department of Health's pilot program for increasing ADR.s through professional educational mailings, use of easy to read forms, presentations to health care professionals, and a series of articles in medical journals. The researchers concluded that physicians can be stimulated to increase their reporting of suspected reactions, thereby improving the viability of the federal reporting system. Scott et al., *supra* note 53, at 1788. The study appears to have guided the development of the MED WATCH program. Many of the methods used in the Rhode Island study were used by the FDA when it launched the program in 1993. *See supra*, note 48 and accompanying text.

Because MEDWATCH reporting is currently voluntary, it may be necessary to consider more stringent measures to obtain reports from health professionals. One suggestion

(continued...)

One objection to relying more heavily on postmarketing surveillance than on premarketing scientific proof of safety and efficacy is that postmarketing surveillance, relying as it does on anecdotal reporting rather than scientific studies, can lead to erroneous conclusions about a drug and to errors in judgment about whether or not to remove a drug from the market.²⁸⁰ Indeed, throughout the crisis with Prozac, Lilly often argued that the reports of suicidal ideation and homicidal tendencies were merely anecdotal and did not prove that Prozac was responsible, because controlled clinical studies were necessary to establish a causal link between violent behavior and Prozac.

While this is true, anecdotal reports do already form the basis of many of the labeling changes that occur for drugs.²⁸¹ Moreover, some researchers have found that informed evaluations of the anecdotal reports at the time they are made can yield good data for a regulatory

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might be to condition the receipt of Medicare funds on full-fledged participation in MIEDWATCH. While such a policy might not influence individual health care providers, it would almost certainly affect a health care organization's policies. HMOs and hospitals would thus become the primary enforcers of MED WATCH reporting. Another suggestion would be to make reporting by individual health care providers mandatory. Such a policy would have problems of enforcement and could result in reports that are uninterpretable, as providers would have an incentive to over-report in order to avoid penalties for failure to report.

280 See G.R. Venning, *Validity of Anecdotal Reports of Suspected Adverse Drug Reactions The Problem of False Alarms*, 284 BRJT. MED. J. 249 (1982) (finding that the validity of anecdotal reports are often challenged on the grounds that they may be false alarms).

281 Kessler, *supra* note 46 (using several specific examples to demonstrate that voluntary reports of adverse drug reactions or product problems has led to warnings to the manufacturer, labeling changes, requirements for postmarketing studies and product withdrawals; also, reporting that lack of reporting can delay problem detection, as with silicone breast implants).

agency to determine the need for action on a drug.²⁸² Venning looked at anecdotal reports received on certain drugs during the initial years of their marketing and compared the anecdotal reports with later verifiable information on the drug's effects in order to determine how often initial anecdotal reports are actually false alarms. The study showed that anecdotal reports yielded 70% true positives, with no absolute proof of false positives.²⁸³ The data also showed, though, that if there was not an informed, commonsense evaluation of each new anecdotal report at the time it was made, then as many as two-thirds of the reports are false alarms, making anecdotal reports meaningless.²⁸⁴ Venning therefore concluded that clear criteria for assessing the reports when they are made could yield good data on which a regulatory agency could base decisions about a drug. Thus, relying heavily on postmarketing surveillance will still ensure that the American drug supply is safe and effective, provided that the postmarketing surveillance system is strong and capable of regularly providing useful information to the FDA.

Finally, the FDA should consider postmarketing surveillance through patient self-monitoring. Relying on the work of Fisher *et al.*, this proposal advocates that the FDA give patients instructions on reporting adverse effects directly to a hotline number and encourage them to do so. Fisher *et al.* designed a study to develop new methods for collecting postmarketing surveillance data from outpatients.²⁸⁵ Patients receiving a new prescription for one of two

²⁸² Venning, *supra* note 280, at 251.

²⁸³ *Id.*

²⁸⁴ *Id.*

²⁸⁵ Seymour Fisher et al., *New Approaches to Postmarketing Surveillance*, 90 PSYCHOPHARMACOLOGY 347, 349 (1986) [hereinafter *New Approaches*].

categories of drugs – tricyclic antidepressants or antibiotics – were asked to participate in the study. Half of the patients were asked to call a toll-free number to report any new or unusual symptoms during the first two weeks of taking the drug. The other half were contacted two weeks after receiving the prescription and were interviewed to determine any adverse drug reactions while taking the medication. The results of the study showed that patient reports are quite reliable.²⁸⁶ In fact, the study detected a previously unknown adverse clinical event associated with one of the antibiotics.²⁸⁷ The small number of patients taking the antibiotic in question prevented a determination as to whether or not the adverse clinical event was in fact an ADR.²⁸⁸ Fisher *et al.* have conducted other studies as well²⁸⁹ and have concluded that what they call the self-monitoring surveillance approach is useful primarily as a signaling method, capable

286 *Id.*

287 *Id.* at 347. Under the terminology used by Fisher *et al.*, adverse clinical events are adverse events that occur during the course of administration of a drug. When an event is classified as an adverse clinical event, it is unclear whether or not the drug is responsible for the event. Once a determination is made as to causation, an adverse clinical event is termed an ADR (adverse drug reaction).

288 *Id.*

289 Seymour Fisher *et al.*, *Postmarketing Surveillance by Patient Self-Monitoring: Trazodone Versus Fluoxetine*, 13 J. CLIN. PSYCHOPHARMACOLOGY 235 (1993) (reporting that patient self-reporting generated a list of adverse clinical experiences associated with fluoxetine use that was not detailed in the labeling information, including suicidal ideation, anger and aggression, and delusions and hallucinations) [hereinafter *Trazodone Versus Fluoxetine*]; Seymour Fisher *et al.*, *Patient Attributions and Postmarketing Surveillance*, 14 PHARMACOTHERAPY 202 (1994) (concluding that patients' judgments as to drug causality can add an independent component to the validity of at least one. . . approach to detecting ADRs) [hereinafter *Patient Attributions*]; and, Seymour Fisher *et al.* *Postmarketing Surveillance by Patient Self-Monitoring: Preliminary Data for Sertraline Versus Fluoxetine*, 56 J. CLINICAL PSYCHIATRY 288 (1995) (comparing patient reports of adverse effects associated with fluoxetine and sertraline, the second of the SSRIs to be marketed, and noting that sertraline, not fluoxetine, had a more troublesome adverse effect profile than fluoxetine) [hereinafter *Sertraline Versus Fluoxetine*].

of obtaining early reliable and accurate postmarketing patient reports about possible side effects.²⁹⁰

Based on the data obtained in the Fisher studies, it is clear that providing a means for patients to report adverse effects on their own is an important supplement to the current postmarketing surveillance system, because obtaining information directly from patients provides reliable and informative evidence of the effects associated with drugs on the market. While patients are theoretically capable of reporting an adverse event through MEDWATCH., the FDA has only encouraged reporting by health professionals.²⁹¹ By establishing a system for patients to report, the FDA could supplement the underreporting by health professionals.²⁹² In tandem, the two systems could provide sufficient information to monitor a drug's safety and efficacy that would allow the FDA to obtain a more complete profile of a new drug in more rapid time.

As these researchers acknowledge, setting up a system would be problematic and costly. The authors themselves say that such a system may not be practical. For example, Fisher *et al* used a thorough interview in their studies, which was designed to make a clear determination at the time of the report that the patient's adverse experience was in fact an ADR. A system that thorough would be complex and costly to start, because of the need for individualized interviews

²⁹⁰ *Sertraline Versus Fluoxetine*, *supra* note 289, at 295.

²⁹¹ *Supra*, notes 55-56 and accompanying text.

²⁹² No system would seem to be capable of providing complete information. Indeed,

Fisher and *et al* note that their studies miss the adverse drug reactions which cause the patient to switch or to be switched from the medication in question to another medication. They also note that they miss those patients who may have become accustomed to an adverse reaction and not reported it. *Sertraline Versus Fluoxetine*, *supra* note 289, at 295.

²⁹³ *New Approaches*, *supra* note 285, at 350.

for each drug on the market.²⁹⁴ Developing the interview material could easily be combined with the sponsor's obligation to submit sample labeling information. The program could spin off of the current MEDWATCH program, making it easier to implement, and could rely on pharmacists to inform patients how to submit reports to the FDA. Alternatively, the reports, combined with the use of the individualized interview, could be made to pharmacists (essentially, pharmacists would operate the hot-line number for patient reporting), who would then relay the information to the

FDA.

One objection that might arise in considering a patient self-monitoring program is that any controversy similar to the Prozac controversy would so taint a patient-reporting surveillance system that the information provided by patients would be more likely to reflect the media hysteria than actual adverse experiences. However, Fisher *et al.* conducted *Trazodone Versus Fluoxetine* in the wake of the Prozac controversy and concluded that patients reporting adverse experiences with fluoxetine were not reacting to media spotlights.²⁹⁵ In fact, after conducting another study of patient self-reporting of adverse effects associated with fluoxetine use, these researchers drew the conclusion that patient self-reporting could have helped to ameliorate the Prozac controversy:

294 Each drug on the market would have an individualized interview designed to elicit information necessary to determine whether or not there is an ADR that would be used when a patient called in an adverse drug experience. This does not seem to be an insurmountable practical problem, given the state of computer technology.

295 *Trazodone Versus Fluoxetine*, *supra* note 289, at 241. The study found that

reports of adverse effects that the media also reported, such as suicidal ideation and aggressive urges, were more frequently reported by trazodone users. The most frequent reports by fluoxetine users reported adverse effects that had never been reported in the media, such as hallucinations and delusions. *Id*

We submit that much of the media circus that created serious public concern during the past few years by spotlighting two widely prescribed psychoactive agents (one a hypnotic, the other an antidepressant) could have been averted if a mechanism for systematically obtaining accurate patient reports had been in place at FDA-approval time, rather than relying on spontaneous reports from physicians, published case reports, or record-linkage systems.²⁹⁶

The most vigorous objection to such a proposal may come from the medical community, arguing that setting up a separate system for patients to report their problems directly to the FDA constitutes government interference with the physician-patient relationship and that any problems with medication should be reported directly to the physician. This objection parallels the strenuous objection raised in response to the FDA's requirement that certain drugs contain patient package inserts (PPIs), which were to provide more information about drugs directly to patients rather than through a physician.²⁹⁷ Critics of the plan for PPIs argued that it would be too costly and would interfere with the practice of medicine. While mandatory compliance with a PPI requirement failed, the debate opened up the voluntary use of PPIs for drugs which present unique safety questions.²⁹⁸ Thus, even if patient self-monitoring is too difficult or costly to implement for all drugs, it could be implemented for certain drugs for which more information would almost certainly be needed. Fluoxetine would have been the perfect candidate for such a

²⁹⁶ *Patient Attributions*, *supra* note 289, at 208. The unnamed references to psychoactive agents are undoubtedly references to Prozac and to Halcion, a sleeping pill that encountered a controversy similar to that of Prozac at about the same time.

²⁹⁷ The FDA issued the requirement on the grounds that patients would be better able to use the drugs safely and effectively and better informed about the risks and benefits of the medication. Hutt and Merrill, *supra* note 8, at 444. A more thorough analysis of the debate over PPIs would provide valuable insights into the feasibility of patient self-monitoring of ADRs. For more information on the debate, see *Id* at 438-50.

²⁹⁸ *Id* at 450.

system. As the first of a new class of antidepressants about which little was understood, patient self-monitoring would have provided additional necessary information that could have helped to determine much earlier how patients responded to the new cluster of side effects and to determine whether or not those responses were dangerous. Moreover, as the data on adverse effects was so limited, patient self-monitoring would have provided additional data needed to develop a more complete and thorough understanding of the side effects associated with fluoxetine use.

Vt. Conclusion

The case of Prozac makes it clear that, at least for antidepressant drugs, reform of the FDA drug approval process could be shortened by decreasing the preclinical and clinical test data required and improving postmarketing surveillance to insure that they are safe and effective in the general population. The case of Prozac has also shown why current reform proposals are insufficient to address the shortcomings of the current system. Finally, this paper has advocated a new approach for deciding how to reform the drug approval process, with the expectation that this approach will yield better results and a more efficient process.

Prozac's story is not unique. Other drugs, such as the controversial sleeping pill Halcion, have experienced the same treatment from the public as Prozac. Also, antipsychotic drugs, used to treat schizophrenia and related illnesses, suffer from having to undergo the same generic approval process that does not account for special issues related to this class of drugs, such as the lack of good animal models of schizophrenia. The arguments developed within this paper, then, apply to more than the limited case of Prozac. Reform of the FDA drug approval process should, therefore, account for those arguments and should be considered in the context of more than just AIDS drugs and drug lag.